ASSESSMENT OF FACTORS THAT PREDICT A POSITIVE CIRCUMFERENTIAL RESECTION MARGIN (CRM) IN RECTAL ADENOCARCINOMA

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT OF THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY FOR THE M.S BRANCH- I (GENERAL SURGERY) EXAMINATION TO BE HELD IN MAY 2019

DECLARATION

This is to declare that the dissertation titled "Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma" in the department of general surgery is my own work, done under the guidance of Dr. Mark Ranjan Jesudason, Professor and Head, Colorectal Surgery, submitted in partial fulfilment of the rules and regulations for the M.S Branch I – General Surgery degree examination of The Tamil Nadu Dr. M.G.R Medical university, Chennai, to be held in May 2019.

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BONAFIDE CERTIFICATE

This is to certify that "Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma" is a bonafide work of Dr. Geethu Rachel Iype, in partial fulfilment of the requirements for the M.S. General Surgery examination (Branch I) of The Tamil Nadu DR M.G.R. Medical University to be held in May 2019.

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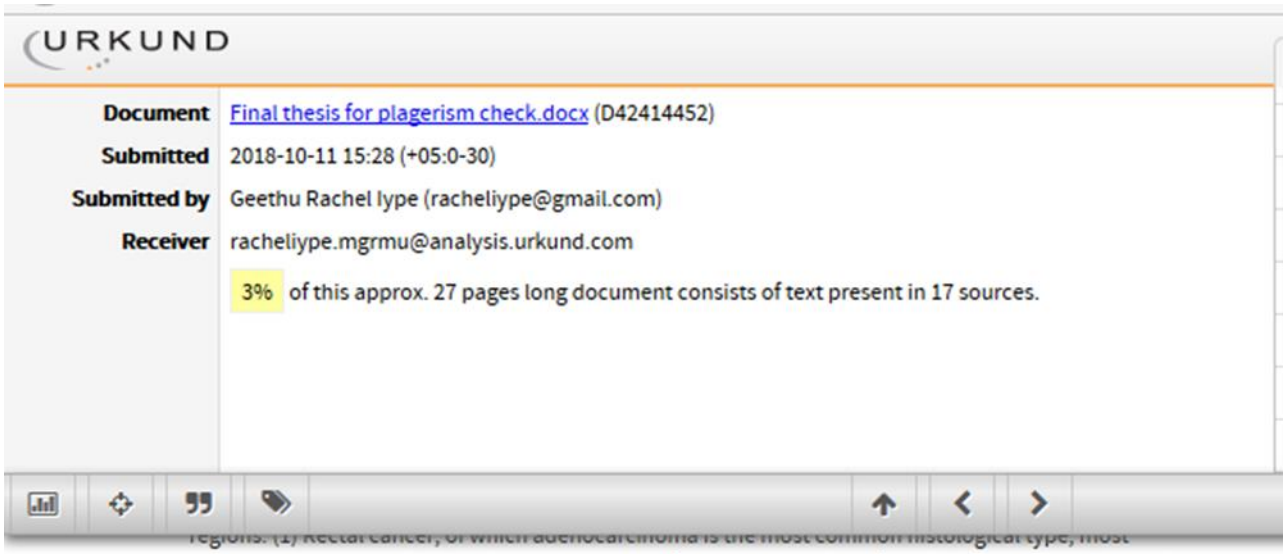

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Submitted	2018-10-11 15:28 (+05:0-30)
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regions. (1) Rectal cancer, of which adenocarcinoma is the most common histological type, most commonly presents with bleeding per rectum, or features suggestive of partial or complete obstruction. Clinical examination and diagnosis would include a thorough history and examination including a digital rectal exam, proctoscopy and sigmoidoscopy. Biopsies are taken from any suspicious lesion and a thorough histological examination is done of the same. Local imaging including MRI of the pelvis to assess the extent of disease and colonoscopy, chest X- ray, contrast enhanced CT abdomen and basic blood investigations are done to rule out systemic spread of the disease are done. The disease is staged according to the TNM classification and a multidisciplinary approach is adopted for further management. Radical resection of the tumour with negative margins remains the mainstay of therapy and in rectal cancer resections the circumferential resection margin has been shown to have the most significant impact on recurrence rates ref). To achieve a negative CRM, down staging of the disease is often necessary, and this is achieved by neo-adjuvant chemo-radiotherapy. A negative CRM (< 1 mm) is known to be one of the most important disease prognosticators for a positive outcome. (2) Various studies have shown that there are multiple tumour specific characteristics and treatment factors that can independently predict a positive CRM. These factors not only provide prognostic value, but can also be recognized as high- risk features that warrant pre-operative recognition and having a potential for alteration of the individual patient's treatment plan. (3) The various factors that can act as predictors of a positive CRM are many. They may be classified as tumour related, patient related and surgical. These include size of the tumour, the 'T' and 'N' stage of the tumour, histologic differentiation, vascular invasion, lymphatic and perineural infiltration, site of the tumour, type of operation, plane of surgery, sex and BMI of the patient, surgeon's experience etc. (4), (5), (6), (7), (8). The modern history of carcinoma rectum and its surgical management with rectal resection dates back to 1826, when Lisfranc attempted resection of the rectum and anus through a perineal approach, with a perineal colostomy. In an attempt to improve access to the upper rectum, Kraske in 1885 developed the posterior approach via the sacrum, while preserving the anal spincters. Czerny in 1884 described the first combined approach, where he completed the perineal dissection from an abdominal approach. In 1908 Sir Ernest Miles described his modification Czerny's operation, which included complete extripation of the rectum and

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Sub: **Fluid Research Grant NEW PROPOSAL:**
Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma.
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Dear Dr. Geethu Rachel Iype,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
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Christian Medical College, Vellore - 632 002.

Cc: Dr Mark Ranjan Jesudason, Dept. of Surgery- 2, CMC, Vellore

ACKNOWLEDGEMENTS

I would like to thank God for entrusting me with this study and for helping me to successfully complete the same.

I express my sincere and heartfelt gratitude to Dr. Mark Ranjan Jesudason, Professor and Head, Department of Colorectal Surgery for the conceptualization of my thesis, for being a patient guide and an enduring mentor, without whose help conception and completion of this project would not have been possible.

My sincerest thanks to Dr. Rajat Raghunath, Assistant professor, Department of Colorectal Surgery, my co guide for his help with providing information, constant motivation, encouragement and guidance in shaping this study through each of its stages.

I would like to thank Dr. Anu Eapen, Professor, Department of Radio diagnosis my co guide for helping me with the interpretation of imaging involved in the study.

I would like to thank Dr. Dipti Masih, Associate Professor, Department of Pathology,

for all the help she provided with the interpretation of pathological specimen reports.

I would lik to thank Dr. Gigi Varghese, Associate Professor, Colorectal Surgery, Dr. Rajesh Joseph Selvakumar, Assistant Professor Colorectal Surgery, and Dr. Bharat Shankar, Assistant Professor Colorectal Surgery, for all the encouragement.

Ms. Tunny Sebastian, my statistician for her timely help and patience with data analysis of my study and for making it easy for me to comprehend.

The institutional review Board (IRB) of Christian Medical College, Vellore for giving me permission for this project.

I offer my gratitude to all the patients, who were part of this study, for their valuable co-operation and enabling me to learn from them.

My gratitude to my family and friends for all the encouragement, patience and support they provided.

Geethu Rachel Iype

October 2018

TABLE OF CONTENTS

1. INTRODUCTION

Colorectal cancer, of which up to 30% may be rectal in origin, is the third most common cancer in the world according to the WHO statistics . It is the second most common cancer among women (9.2%) and third most common in men (10.0%) world over (1). Though traditionally a disease of the more affluent civilizations, a 45% incidence of disease is noted in the poorer nations of the world. Also of note is the fact that mortality due to the disease is higher in the poorer nations, a reflection of the poorer prognosis of the disease in these regions.(1)

Rectal cancer, of which adenocarcinoma is the most common histological type, most commonly presents with bleeding per rectum, or features suggestive of partial or complete obstruction. Clinical examination and diagnosis would include a thorough history and examination including a digital rectal exam, proctoscopy and sigmoidoscopy. Biopsies are taken from any suspicious lesion and a thorough histological examination is done of the same. Local imaging including MRI of the pelvis to assess the extent of disease and colonoscopy,

chest X- ray, contrast enhanced CT abdomen and basic blood investigations are done to rule out systemic spread of the disease are done.

The disease is staged according to the TNM classification and a multidisciplinary approach is adopted for further management. Radical resection of the tumour with negative margins remains the mainstay of therapy and in rectal cancer resections the circumferential resection margin has been shown to have the most significant impact on recurrence rates ref). To achieve a negative CRM, down staging of the disease is often necessary, and this is achieved by neo-adjuvant chemo-radiotherapy. A negative CRM (> 1 mm) is known to be one of the most important disease prognosticators for a positive outcome.(2)

Various studies have shown that there are multiple tumour specific characteristics and treatment factors that can independently predict a positive CRM. These factors not only provide prognostic value, but can also be recognized as high- risk features that warrant pre-operative recognition and having a potential for alteration of the individual patient's treatment plan.(3) The various factors that can act as predictors of a positive CRM are many. They may be classified as tumour related, patient related and surgical. These include size of the tumour, the 'T' and 'N' stage of the tumour, histologic differentiation, vascular invasion, lymphatic and perineural infiltration, site of the tumour, type of operation, plane of surgery, sex and BMI of the patient, surgeon's experience etc.(4),(5),(6),(7),(8). Here in this study we are looking at some of these factors and the feasibility of using them as predictive factors.

2. AIMS AND OBJECTIVES

AIM : The aim of the study is to assess the factors that predict a positive Circumferential Resection Margin in rectal adenocarcinomas.

PRIMARY OBJECTIVE: To determine if the T stage of the tumour can predict CRM positivity in adult patients undergoing rectal resection for adenocarcinoma rectum in the Colorectal Surgery Unit in CMC Vellore between 2016 and 2018.

SECONDRY OBJECTIVE: To determine if others factors like the distance of the lower margin of the tumour from the anal verge, the position of the tumour as predominantly circumferential, lateral, anterior or posterior, the gender of the patient, the Body Mass Index of the patients, extra mural venous invasion (EMVI), CRM positivity on MRI and the histology of the tumour can predict the CRM positivity in the above mentioned group of patients.

3. REVIEW OF LITERATURE

3.1 HISTORY AND EVOLUTION

The earliest documented diagnosis of carcinoma rectum is from ancient Egyptian mummies of the Ptolemaic period (BC 200–400) (8). The modern history of carcinoma rectum and its surgical management with rectal resection dates back to 1826, when Lisfranc attempted resection of the rectum and anus through a perineal approach, with a perineal colostomy. In an attempt to improve access to the upper rectum, Kraske in 1885 developed the posterior approach via the sacrum, while preserving the anal spincters. Czerny in 1884 described the first combined approach, where he completed the perineal dissection from an abdominal approach. In 1908 Sir Ernest Miles described his modification Czerny's operation, which included complete extripation of the rectum and anus and the surrounding lymphatics, in what came to be known as the concept of abdomino-perineal excision (APE) or the Miles operation. Though Miles concept was oncologically sound, it was an extremely morbid operation with mortality rates as high as 42%. Henri Hartmann in 1928 described rectal resection for upper rectal tumours via only an abdominal approach in what was initially a two

staged operation , with maturation of an end stoma initially , followed by rectal resection. (9)

Over the next few decades with the modifications in intra, pre and post operative care the mortality and complications with rectal cancer surgery improved significantly.. Total mesorectal excision (TME) for carcinoma of the rectum was popularised in the late 1980s by William Heald. The technique involved sharp dissection to perform the complete excision of the mesorectal and its associated lymphatics along the subtle fascial planes that encompass the rectum. To reduce the local recurrence, the zone of downward spread within the mesorectum was described. Off late, local excision is being combined with neo-adjuvant and adjuvant chemo-radiotherapy to maximize local control with a minimally invasive approach.

3.2 EPIDEMIOLOGY

Colorectal cancer is the third most common cancer in the world. Over a hundred thousand new cases are diagnosed globally every year. CRC accounts for about 8% of all cancer related deaths in the world, thus making it the fourth most common cause for cancer related deaths. The Annual Incidence Rates for rectal cancer in men in India is 4.1 per 100,000 thus making it the 9^{th} most common cancer among men. The incidence among women in the country is much lower, though globally it is the second most common when combined with colon. The highest annual incidence in the country for men was recorded in

Thiruvananthapuram(4.1)and for women was in Nagaland (5.3) as per reports published in 2013. (10) The incidence rates are generally higher in the western population with age over 50 worldwide, but in a disturbing trend, latest studies have shown a rising incidence in the young people in in some population based studies. There is also a rising trend in the incidence of CRC in developing countries like India and Brazil. This can probably be attributed to the increasingly urbanized lifestyle and environment with low physical activity, high calorie - low fibre diet becoming popular in these countries. Another alarming fact is ratio of death to incident cases in India – above 70% while in Japan it is 42% and an even lower 32% in the United States. In India five year survival rates are almost half in the rural areas as compares to urban areas, indicating inadequacies in initial diagnosis treatment and follow up in the rural regions.(11)

3.3 AETIOLOGY AND RISK FACTORS

Various studies have concluded that tumours of the colon and rectum have similar genetics and other characteristics; hence they can be clubbed together. Various genes are associated with the same and so are certain syndromes.(10)

3.3.1 ENVIRONMENTAL FACTORS

3.3.1.1 GEOGRAPHICAL VARIATIONS

There is global variation in the incidence rates of rectal cancers in the world. The highest incidence is noted in developed countries whereas low incidence is from developing countries. But as migrants from low incidence developing countries go to areas of high incidence and mix with the high risk population, their risk of developing colorectal cancer becomes the same as that of the resident population.. Over the last 50 years there is significant increase in the risk of development of colorectal cancer in the low risk countries and this can be attributed to the changes in lifestyle, diet and migration to high risk areas.

3.3.1.2 DIETARY FACTORS:

According to the European Prospective Investigation into Cancer (EPIC) and

Nutrition study there is significant relationship between diet, lifestyle, genetic and environmental factors. There is association between rectal cancer and increasing processed or fresh red meat consumption .(12) Fish and dietary fibre was found to be protective. EPIC has also concluded that fruit and vegetable intake can be protective. Low dietary fibre is associated with increased risk of rectal cancer.

3.3.1.3 LIFESTYLE:

Alcohol consumption of 30-45g/day increases risk of development of colorectal cancer by 16%. Consumption more than 45g/day increases the risk by 41% (13).

Obesity increases risk of colorectal cancer . Tobacco smoking negates the benefits

of anti-oxidation by fruits and vegetables, but there is no definite conclusion that smoking increases the risk of rectal cancer (12).

3.3.1.4 OTHER FACTORS:

• *Ulcerative colitis* has been known to be associated with increased risk of developing colorectal cancer. It is associated with the time duration from the onset of the disease and duration of active colitis. Earlier the onset of disease, higher is the chance of malignant transformation .(14)

• *Immunosuppression* post organ transplantation, long term steroid intake and steroid abuse are known to increase the risk. (10)

• *Diabetes mellitus associated with insulin resistance*: Studies have shown an association of insulin-like growth factors with the development of colorectal cancers.(14) (15)

• Use of *androgen deprivation therapy* like orchiectomy is associated with increased risk of colorectal cancer.

• *Uretero- colic anastomosis* is known to have high risk of development of colorectal cancer due to chronic irritation of the mucosa with urine.

• *Ethnicity* : the African –American community is known to be at a higher risk.

• Other factors include history of cholecystectomy, acromegaly, HIV infection, prior treatment for Hodgkins lymphoma etc.(10)

3.3.2 GENETIC FACTORS AND HEREDITARY CRC SYNDROMES:

Almost 5% of all colorectal malignancies can be attributed to hereditary factors. This can be broadly divided into two groups – those associated with colonic polyposis and those not associated with colonic polyposis. Those associated with

colonic polyposis include FAP or familial adenomatous polyposis(FAP), its variants -Turcot,

Gardner, and attenuated FAP, and MYH-associated polyposis. The non-colonic polyposis category mainly consists of Hereditary non polyposis colon cancer (HNPCC) or Lynch syndrome. Peutz Jeghers syndrome is another association with colorectal cancer.

3.4 ANATOMY OF THE RECTUM

The rectum forms the last part of the large intestine, between the sigmoid colon and the anal canal. Embryological development of the rectum, up to the dentate line is from the hind gut which is endodermal in origin. The distal part of the rectum and its continuation, the anal canal is ectodermal in origin, being derived from the cloaca. Anatomically the rectum is located in the posterior part of the true pelvis and extends from the recto-sigmoid junction at the level of the third sacral vertebrae and extends upto the ano- rectal junction as marked by the dentate line. Surgically though, the rectum is considered to begin at the point where the taeniae coli coalesce and end at the muscular ano-rectal ring and is around 12 -15 cm long. In the course of the rectum are two antero- posterior curvatures – the concavity of the sacrum and the posterior bend at the perineal flexure. There are three lateral curvatures, the upper and lower being convex to

the right and the middle which is convex to the left. The mucosa of the rectum falls into folds known as the valves of Houston and they are three in number.

The rectum can be divided into three parts with respect to anatomy

Upper third - mobile and has a peritoneal covering anteriorly and laterally.

Middle third - peritoneum covers the anterior and part of the lateral surfaces.

Lowest third - Lies deep in the pelvis and is surrounded by fatty mesorectum and fascial layers (Denonvilliers' fascia, Waldeyer's fascia). It is completely devoid of peritoneal covering. These fascial layers are a barrier to malignant invasion and form the basis of total mesorectal resection and circumferential resection margin.

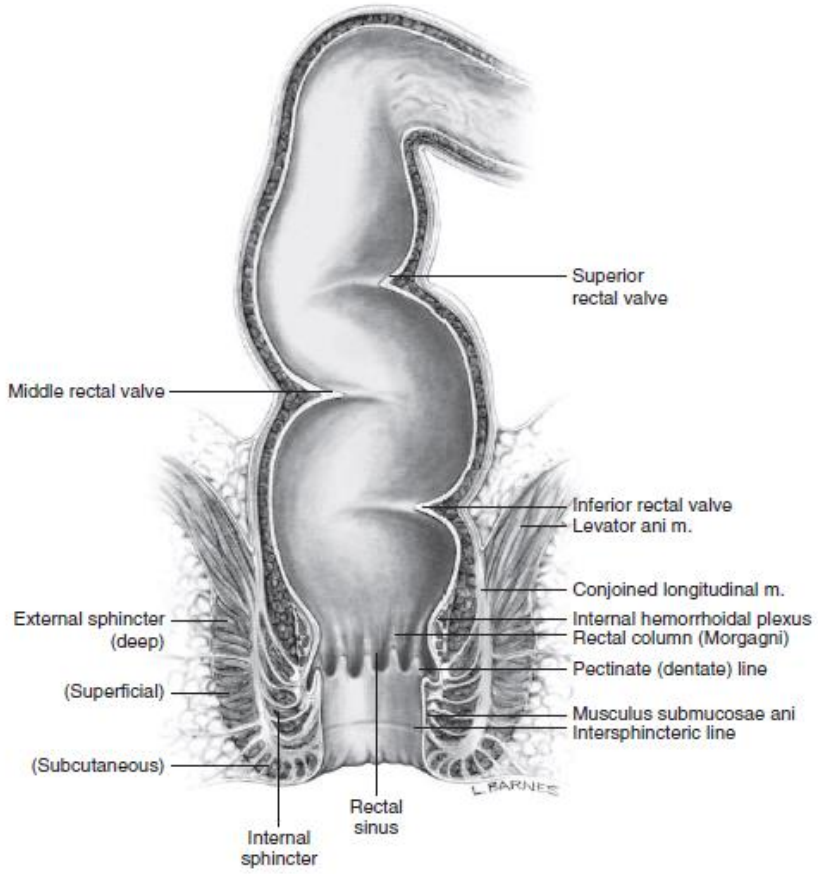

Figure 1: Anatomy of the Rectum

In males, anteriorly the upper 2/3rd of the rectum is related to the rectovesical pouch and the lower 1/3rd to the base of the urinary bladder, terminal ureters, seminal vesicles, the ductus deference and the prostate.

In females the upper 2/3rd is anteriorly related to the recto-uterine pouch, which separates it from the uterus and upper 1/3rd of the vagina. The lower 1/3rd is related to the lower part of the vagina.

The posterior relations of the rectum are the same in both male and females. It is related to the lower three sacral vertebrae ,the coccyx and the ano coccygeal ligament, the pyriformis, the coccygeus and levator ani muscles, the median sacral, superior rectal and lower lateral sacral vessels, the sympathetic chain, the pelvis splanchnic nerves, lymph nodes, lymphatics and fat.

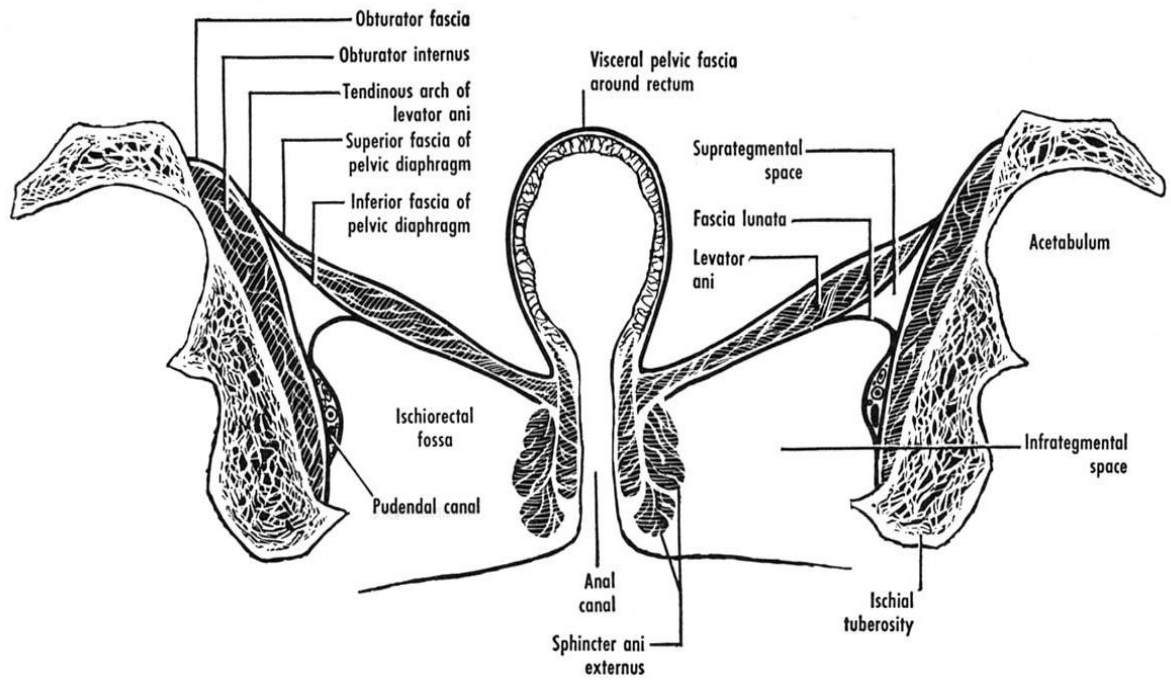

Figure 2: Anatomy of the Pelvis

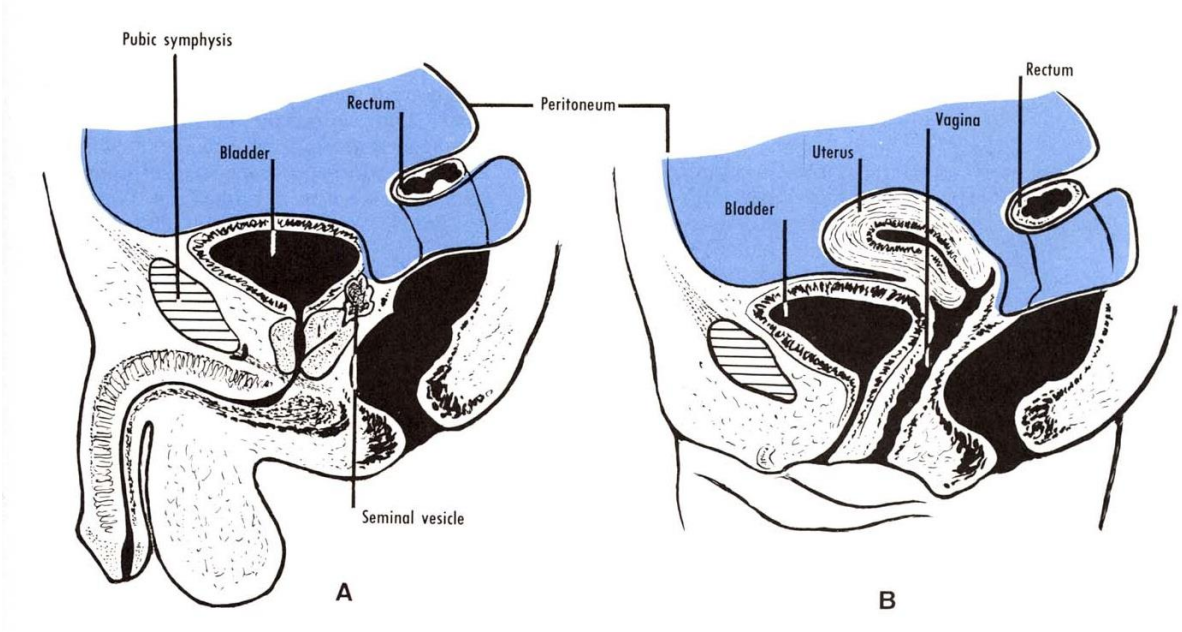

Figure 3: Difference in A) Male and B) Female pelvic anatomy

3.4.1 BLOOD SUPPLY

The primary arterial supply of the rectum is from the superior rectal artery, which arises from the inferior mesenteric artery. It also receives blood supply from the middle rectal, a branch of internal iliac and the inferior rectal, a branch of the internal pudental artery. There is a rich network connecting the terminal arteriols, thus making the rectum very resistant to ischemia.

The venous drainage is by the superior rectal vein , which drains into the inferior mesenteric vein , which ultimately joins the portal circulation. The middle rectal vein drains the rectal ampulla and empties into the systemic circulation via the internal iliac veins.

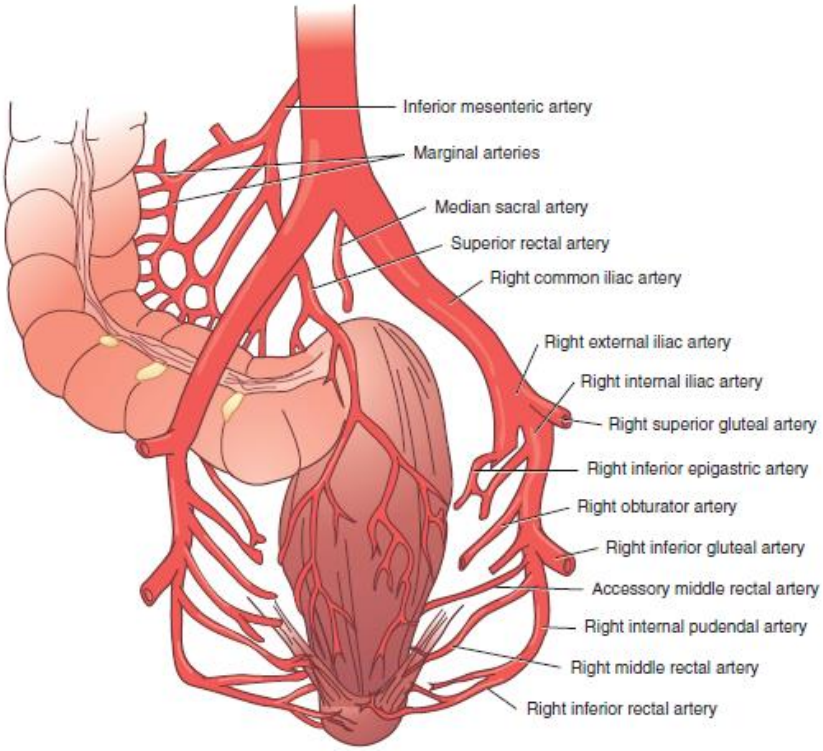

Figure 4: Arterial supply of the rectum

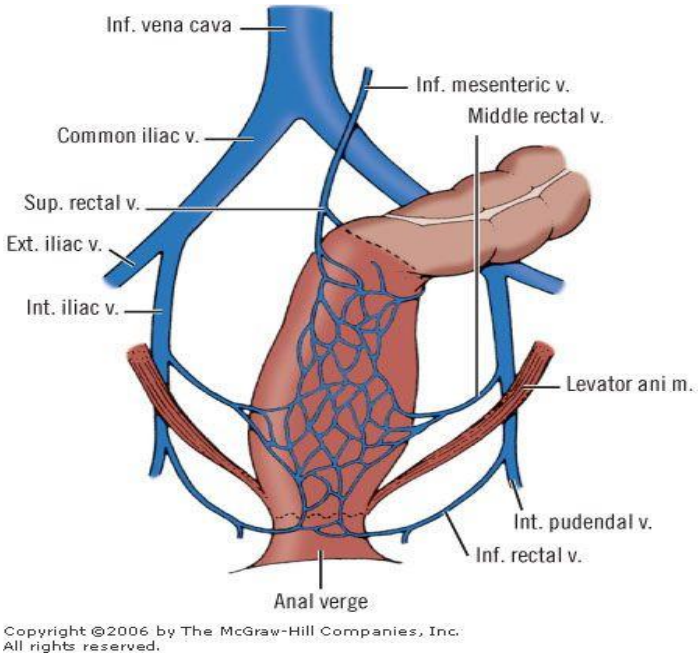

Figure 5: Venous supply of the rectum

3.4.2 LYMPHATIC DRAINAGE

The lymphatic drainage follows the arterial supply in case of the rectum. There is a rich network of lymphatic capillaries in the rectal wall that drain them into external lymphatic channels. The upper 2/3rd drains into the inferior mesenteric and paraaortic nodes through the pararectal and sigmoid nodes. The lower 1/3rd of the rectum drains into the internal iliac and superficial inguinal node basin.

The flow of lymph dictates the clearance of nodes and thus requires a high proximal clearance of nodes in rectal resection. Pelvic side walls develop lymphatic metastases when the upward direction of the lymph flow is obstructed either mechanically by the tumour or due to the emboli.

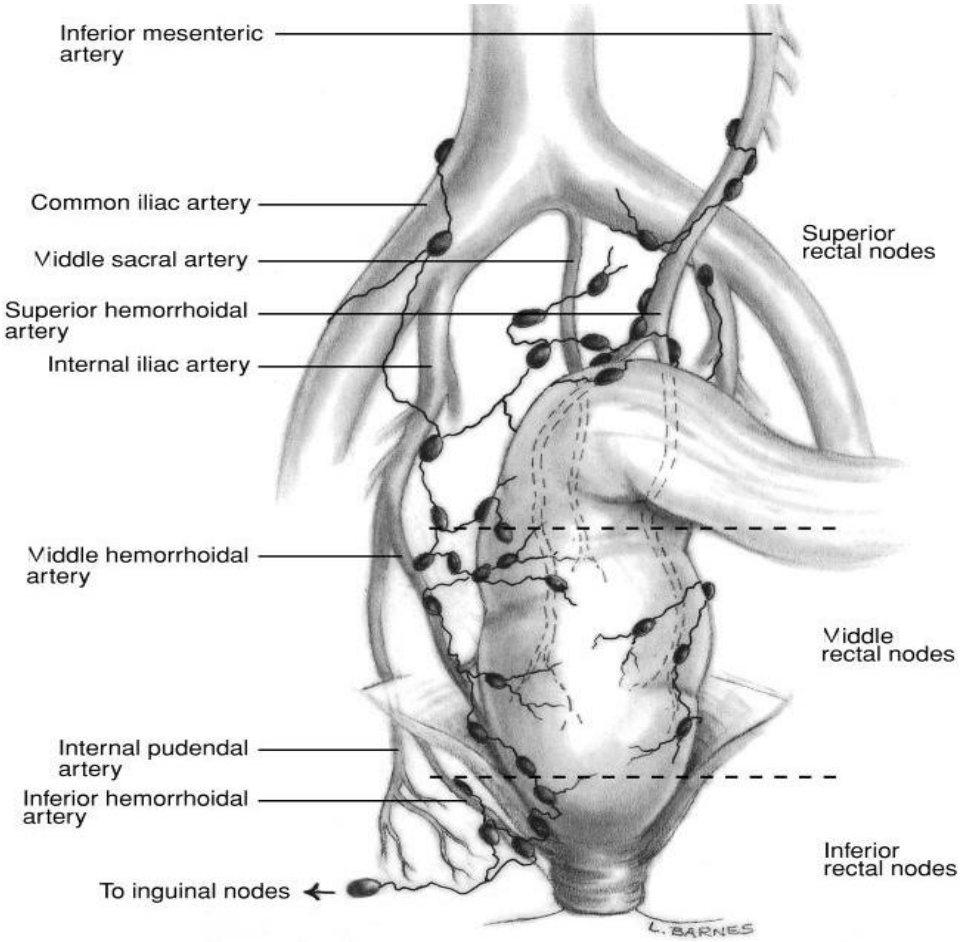

Figure 6: Lymphatic drainage of the rectum

3.4.3 NERVE SUPPLY

The rectum is supplied by both sympathetic and parasympathetic systems. The sympathetic supply comes from the pre ganglionic lumbar splanchnic from L1 to L3 and synapse at the pre aortic plexus. They are vasoconstrictor and inhibitory to the rectal muscles and give motor supply to the internal sphincter.

The parasympathetic nerve fibres are known as the *nervi erigentes* . They originate from S2-S4. These fibres join the sympathetic fibres to form the pelvic plexus. The sensation of rectal distension and pain are carried by the parasympathetic supply. The motor fibres control the external sphincter. Rectal resection may lead to disruption of the pelvic plexus, and can result in neurogenic bladder and sexual dysfunction.

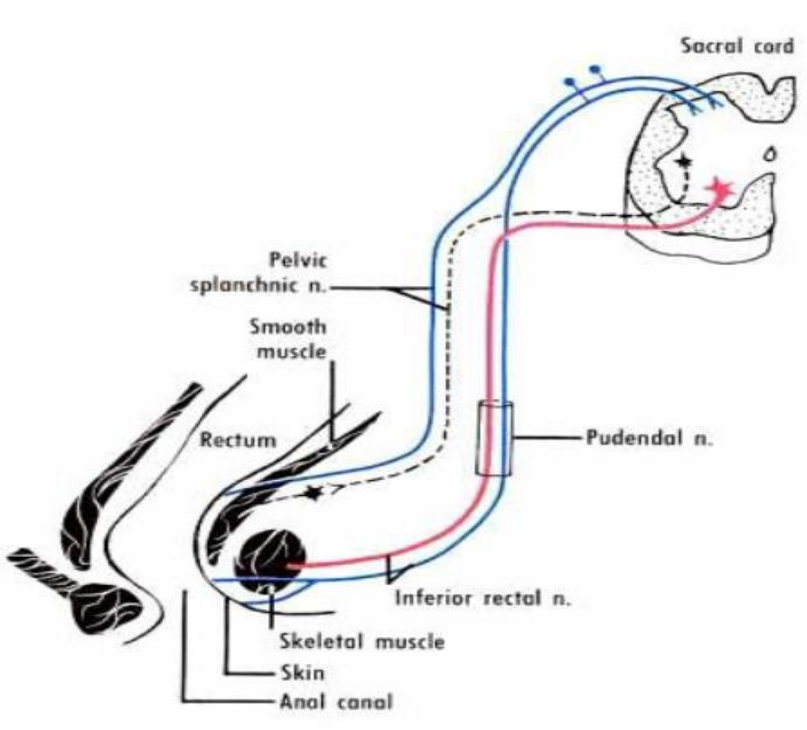

Figure 7: Nerve supply of the rectum and anal canal.

3.4.4 HISTOLOGY

The rectal wall is composed of the following layers.

The *mucosa*, which has the epithelium - simple or stratified columnar and is thrown into large folds and contains abundant goblet cells. The lamina propria which contains lymphatics and cappilaries, and the muscularis mucosa, a thin irregular layer.

The *submucosa*, which is a layer of loose connective tissue that contains the capillary and nervous plexus.

The *muscularis externa or muscularis propria* which has an outer longitudinal coat and inner circular coat of muscles.

Serosa is present only in the upper part of the rectum while the lower part is surrounded by adventitia.

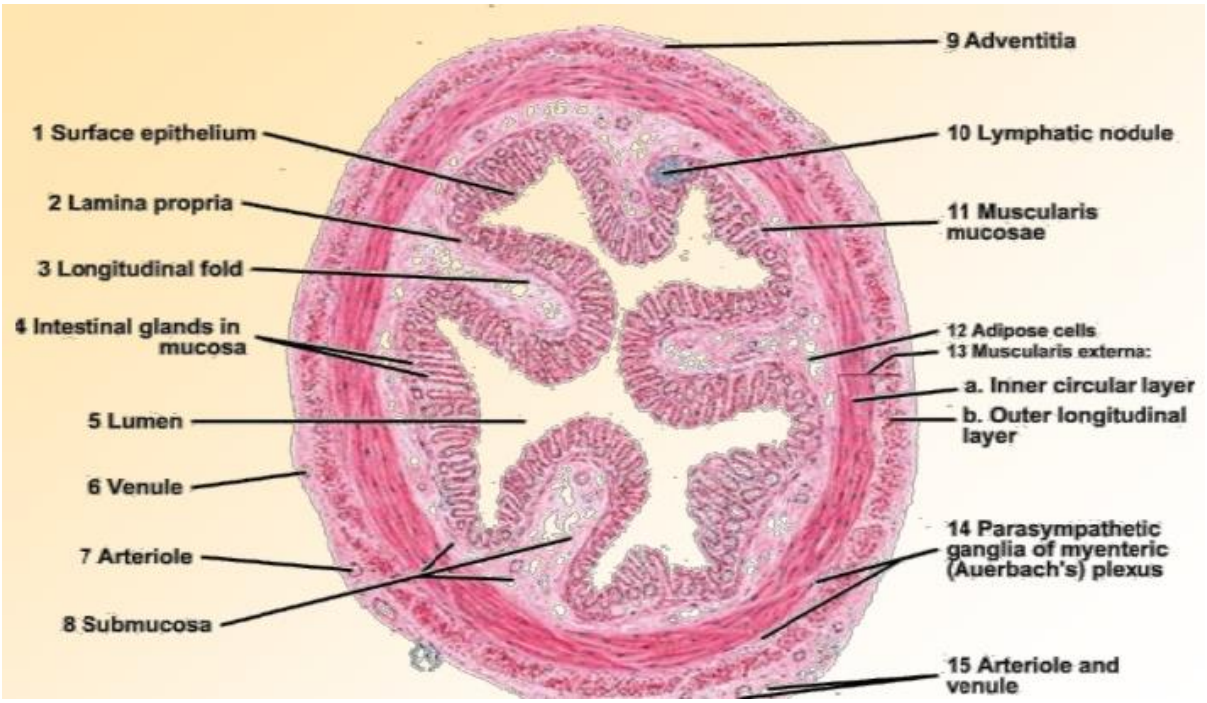

Figure 8: Normal histology of the rectum

3.5 ADENOCARCINOMA – THE PATHOLOGY

The most common form of cancer affecting the rectum is adenocarcinoma, (90%) which arises from the glandular epithelial cells. Other rarer types include neuroendocrine tumours, squamous cell, spindle cell etc. The histological tumour grading of adenocarcinoma is based on glandular formation. It is classified as well differentiated, moderately differentiated and poorly differentiated. In well differentiated adenocarcinoma, more than 95% of the tumour is gland forming. In moderately differentiated tumours, 50 to 95% of the bulk is gland forming , while in poorly differentiated, the tumour is mostly solid, with less than 50 % glandular formation.

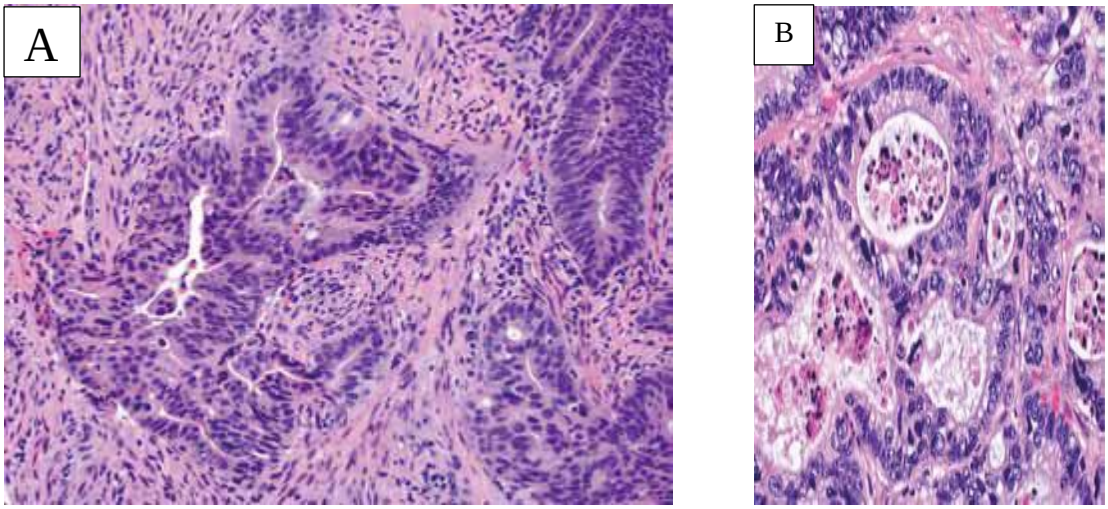

Figure 9:(A)Moderately differentiated adenocarcinoma with glandular structure and desmoplastic reaction x 200 (B) Necrotic debris in the lumen of glands x400

About 70% of all diagnosed colorectal adenocarcinoma are moderately differentiated.

Poorly differentiated tumours are otherwise classified as high grade and are considered as an independent risk factor for poor prognosis, translating to poor patient survival. In contrast to the other parts of the gastrointestinal tract, for a diagnosis of invasive carcinoma of the colorectum to be made, there should be invasion of the submucosa. Other features commonly seen on histology include presence of desmoplasia and characteristic necrotic debris in the glandular lumen, known as “dirty necrosis”.

Various other subtypes of carcinoma of the colo-rectum are mentioned in the WHO classification. The more important and significant in terms of prognosis include the mucinous adenocarcinoma and signet ring cell adenocarcinoma. Signet rig cell adenocarcinoma is a rare entity, making up only 1% of the total type. It is identified as above when more than 50% of the cells show signet ring features - a peripheral nucleus with a large intra-cytoplasmic mucin vacuole. Though it makes up only 1% of all the adenocarcinomas, its significance lies in the fact that it carries a worse outcome than the conventional adenocarcinoma, and is classified under the poorly differentiated, high grade carcinoma.(16)

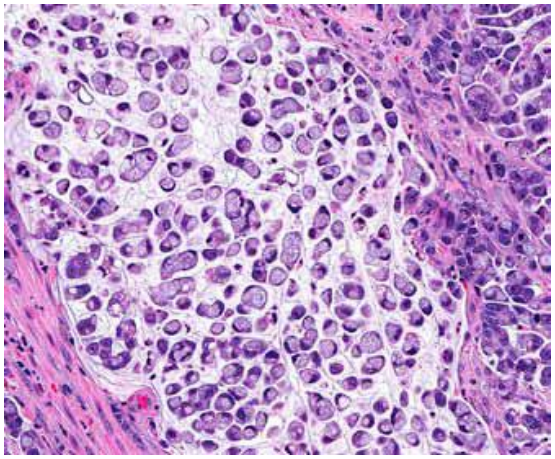

Figure 10: Signet ring cell adenocarcinoma

3.5.1 THE ADENOMA CARCINOMA SEQUENCE

The adenoma- carcinoma sequence is widely recognized as the series of events through which most colorectal cancers develop. Various clinical and epidemiological evidence suggest that colorectal carcinoma develops through a progression of benign polyp into invasive carcinoma and genetic pathways have been elucidated, demonstrating the same. Though de novo genesis of small adenocarcinomas have been documented, a majority of the carcinomas develop from pre existing adenomas. This has .This also helps us to prioritise management of colo-rectal adenomas, and their implicit relationship to prevention of rectal cancer development. (17)

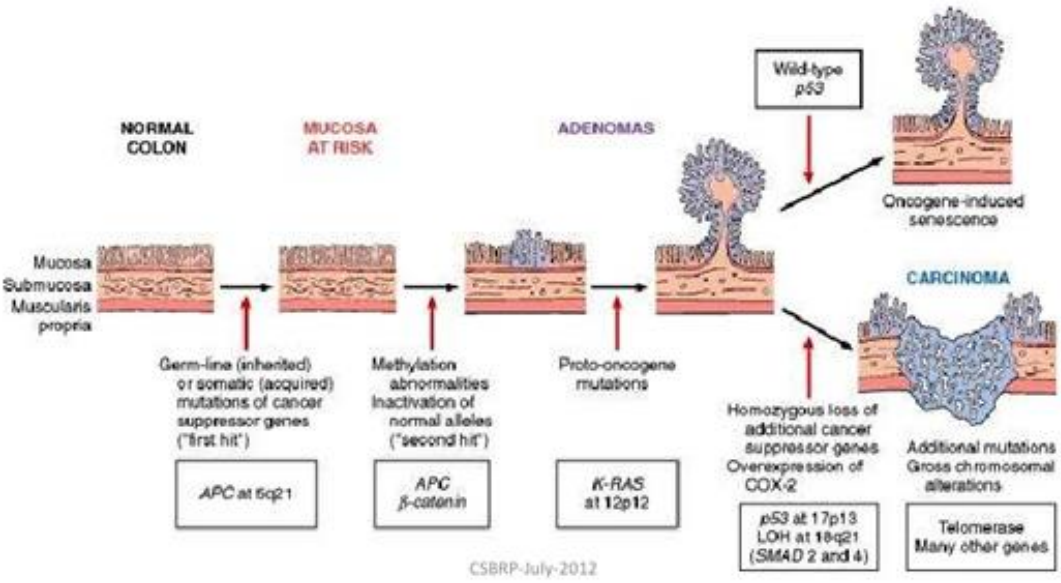

Figure 11: Molecular model of the adenoma carcinoma sequence

3.5.2 STAGING OF RECTAL CANCER

Staging of cancer serves the purpose to describe the anatomic extent of the lesion. Staging is done by clinical examination, radiology, and pathology. Staging facilitates the planning of treatment, assessment of tumour response to treatment and prognostication. Dukes' and TNM staging systems are the two most commonly used staging tools in colorectal cancers.

Cuthbert Dukes' published his staging system in 1932 based on cases managed at St. Mark's Hospital London. He classified tumours by pathological local tumour invasion into the following four groups:

A – Confined to rectal wall

B – Breached extra rectal tissue

C – Presence of lymph nodal metastases

D – Distant metastases

Presently, the most accepted staging system for rectal cancer worldwide is the TNM classification system. In 1987, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUC) introduced the TNM staging system for colorectal cancer. This system has undergone several modifications over the past several years and was last updated in 2010 to the current form. The TNM staging system is based on tumour invasion, lymph nodal involvement and distant metastases.

A "y" prefix to TNM indicates that it is the post neo-adjuvant therapy staging, while "p" as a prefix indicates that it is the histo-pathological staging done on the resected specimen.(18)

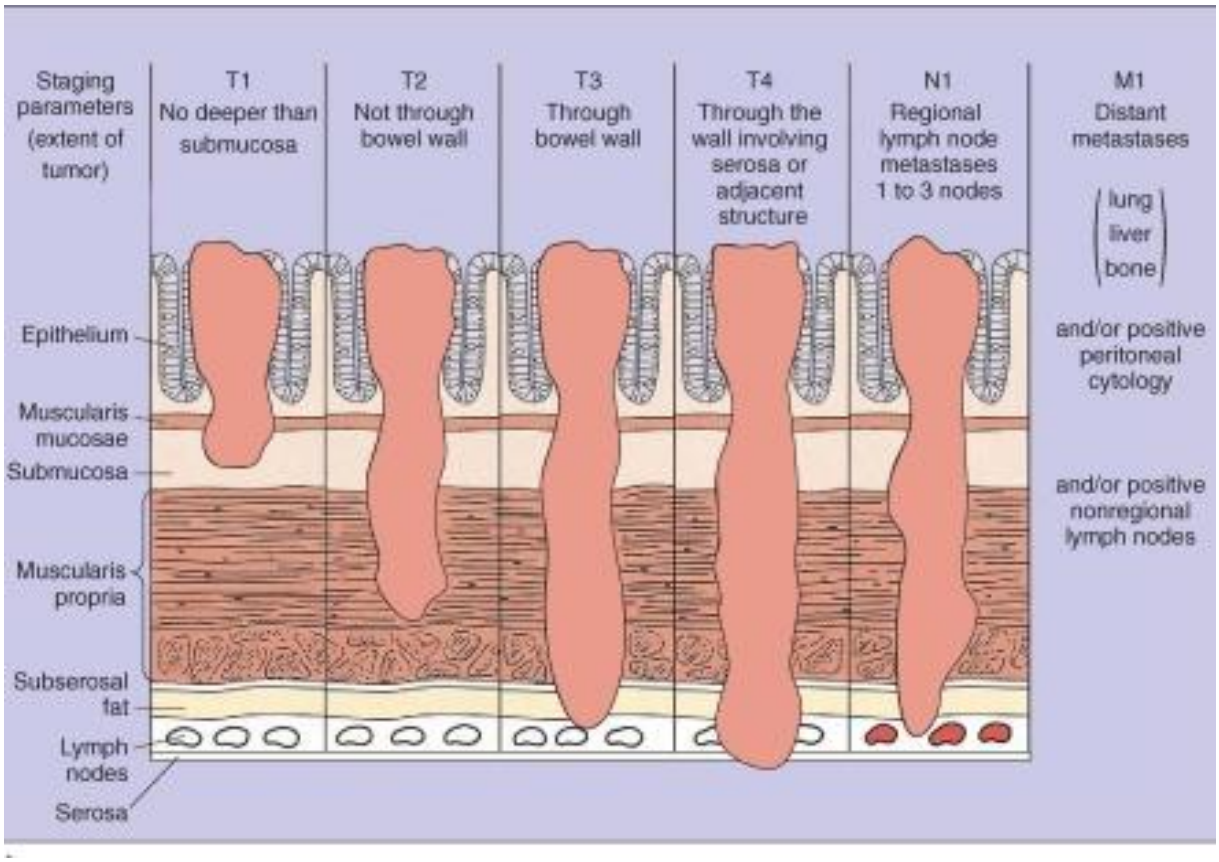

Figure 12: TNM Staging of Colorectal cancer

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum[2]
- **T4b** Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
- **N1a** Metastasis in one regional lymph node
- **N1b** Metastasis in 2–3 regional lymph nodes
- **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
- **N2a** Metastasis in 4–6 regional lymph nodes
- **N2b** Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- **M1b** Metastases in more than one organ/site or the peritoneum

ANATOMIC STAGE/PROGNOSTIC GROUPS					
Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Figure 13: TNM staging of colorectal cancer as per AJCC 7

3.6 PRINCIPLES OF MANAGEMENT OF ADENOCARCINOMA RECTUM

A clinical suspicion of carcinoma rectum is raised based on symptoms and signs after a thorough history and physical examination. The diagnosis is confirmed by an endo-luminal examination and biopsy. Imaging modalities are made use of, to stage the disease and plan the course of management.

The management of rectal cancers have evolved through the ages, with advancement in technology. Though operative management continues to be the mainstay, a multidisciplinary approach is the norm of the day. A multidisciplinary team including surgeons, medical and radiation oncologists, radiologists and palliative care physicians are involved in the process of planning management for these patients. Different patients in various stages of the disease may be treated with an operation, along with chemo-radiotherapy either as neo adjuvant or as adjuvant therapy if required. The treatment is often modified, taking in consideration the age and physical performance status of the patient.

3.6.1 WORKING UP A PATIENT WITH CARCINOMA RECTUM

A comprehensive history of the symptoms including bleeding per rectum and personal and family history must be documented. A thorough physical examination should be done including a digital rectal examination and proctoscopy. Basic blood tests including haemoglobin, renal and liver function

tests and CEA (carcino embryonic antigen) and in some places CA 19.9 are done.(19) A colonoscopy is required, to obtain biopsy and to rule out synchronous lesions and polyps. A histological confirmation is essential before definitive therapy is embarked upon. In an ideal case scenario, the following radiological studies are recommended (24). An MRI of the pelvis with rectal coils if available, to detect the extend of the disease in the pelvis, along with an endoluminal ultrasound study(20). An CT Chest to rule out any lung nodules is ideal, though many centres do a chest X –Ray and follow it up with a CT scan only in case of suspicion. A CECT of the abdomen, including a triphasic study of the liver is mandatory to rule out and intra -abdominal spread of the disease. PET CT scans are usually recommended in case of suspected recurrence at follow up(21) .

All the mentioned investigations help in determining the accurate stage of the disease pre operatively, and thus help the multi -disciplinary team in forming a plan regarding further management. The primary modality of treatment remains operative, with the goal being complete resection of the tumour, with clear margins. Due to the anatomic location of the rectum in the bony pelvis, obtaining a wide clear circumferential margin is technically difficult, both due to accessibility and adjacent organs. Therein lies the role of neo-adjuvant chemoradiation therapy.

3.6.2 NEO-ADJUVANT THERAPY

The advantages for using neoadjuvant chemoradiation are many. Radiation therapy sensitises the tissues to respond better to the chemotherapeutic agents. With combined chemoradiation higher doses of chemotherapy are delivered. It potentially downstages the disease to achieve a pathologic complete response in 15–30% of patients and a partial response in another group. Down staging the tumour facilitates higher chances of obtaining a negative resection margins. Also it aids in planning a sphincter- preserving operation. Other advantages of neo-adjuvant chemoradiation include preventing development of radiation enteritis. Pre-operative radiation prevents radiation of anastomosis and small bowel radiation in the pelvis. Since the neo-adjuvant chemo-radiation is before the operation compliance among patients is better. There are trials which show that preoperative radiotherapy followed by total mesorectal resection results in decreased risk of recurrence when compared with only operation. Dutch Colorectal Cancer Group demonstrated 8% risk of recurrence in patients who underwent only resection and no neo-adjuvant radiation(22) . The Swedish trial demonstrated benefit of survival in subjects receiving preoperative radiation as compared with surgery alone (48%)(23) (24). The Swedish trial also demonstrated 27% recurrence in the surgery-alone group. Studies have concluded that preoperative radiation therapy plus surgery compared with surgery alone significantly reduced the 5-year overall mortality rate, cancer related mortality rate, and local recurrence rate.(24)

The benefits of radiation in rectal cancer as neo-adjuvant therapy are:

• The local recurrence of tumour decreases post curative resection

• With concurrent chemotherapy radiation treats the locally advanced disease to downstage the disease for future resection

• To convert an abdomino- perineal excision which requires a permanent stoma, to a sphincter preserving surgery like low anterior resection

• Palliation of pain, bleeding and perineal discharge. Obstructive and diarrheal symptoms do not respond to local radiation and require surgical intervention like a bypass colostomy if disease is not resectable.

Evidence on reduction of local recurrence of disease after radiation is very strong and it is strongly recommended for locally advanced disease which is not amenable to resection with adequate margins. Few meta analysis have also documented the superiority of pre operative radiotherapy to adjuvant radiation.

Radiation can be administered in many ways. Conventionally, long course chemoradiation is given as a total dose of 45 -50.4 Gy in daily divided fractions (20 – 25 fractions). Concurrent chemotherapy of five cycles is administered along with it. In Europe, short course chemotherapy is popular and is given as 25Gy in 5 fractions. This is followed by surgery.

3.6.3 RECTAL CANCER SURGERY- GOALS

The aim of surgical resection or excision in rectal cancer is to completely remove the tumour with an adequate margin of normal tissue, along with a complete clearance of the draining lymph nodes. This includes excision of the excision of the mesorectal tissue and according to the loco-regional blood supply.

Sphincter sparing operations and re-establishment of bowel continuity at the time of operation has become routine. In spite of attempts to maintain bowel continuity and continence, some patients may require permanent stomas in order to achieve oncologically adequate operations. Counselling these potential patients for the same pre operatively is of utmost importance, as it involves significant change in their life style.

The bony confines of the pelvis and close planes with urinary bladder, prostate and seminal vesicles limit dissection of the distal part of the rectum. In women the limitation is due to the proximity of vagina in the pelvis. Achieving adequate margins in this confined space is of utmost importance to patient survival and quality of life, and at the same time a technical challenge for the operating surgeon.

3.6.3.1 RESECTION MARGINS

• **Distal margin**

Those tumours that are situated between 15 cm from the anal verge and above the puborectalis sling on clinical examination or endoscopy are termed as rectal tumours. These cancers are divided into upper, mid and lower rectal tumours based on the distance of tumour from the anal sphincter.

Upper rectal tumours: 11 – 15 cm from the anal verge
Mid rectal tumours: 6 -10 cm from the anal verge
Lower rectal tumours: less than 6 cm from the anal verge

Anterior resections – sphincter sparing operations, are performed for upper and mid rectal tumours whereas abdomino-perineal excisions are done for low rectal tumours, where continence cannot be preserves and hence the patients require permanent stomas. The choice of operative procedure performed ultimately depends on patient and tumour characteristics. There is no conclusive evidence regarding the adequate distal resection margin for rectal cancer and it is still a topic of controversy. A margin of 5cms distally is traditionally accepted, although several studies have shown that a margin of 1 cm does not translate to higher rates of recurrence.

Within the lumen tumour spreads to within 2 cm unless it is a poorly differentiated tumour or is an aggressive tumour with systemic metastases. The

National Surgical Adjuvant Breast and Bowel Project highlighted the fact that there was no significant difference in survival or local recurrence on comparing distal rectal margins of less than 2, 2 – 2.9, and greater than 3 cm. Hence it highlighted that a 2 cm distal margin is acceptable for resection of rectal carcinoma.

Rectal cancers spread upwards along vascular pedicles and also laterally. Hence removal of draining lymphatics along vascular pedicles is of significance.
Though distal margin is still a topic of controversy, a proximal margin of 5 cm is the recommended standard.

• **Radial margin – Circumferential Resection Margin or CRM**

The radial margin, or what in case of rectal tumours is more commonly known as the circumferential resection margin has been proven by various studies to be an independent factor that determines loco-regional recurrence and overall survival of the patient. The importance of a negative circumferential resection margin, more than a negative proximal or distal margin has been stressed upon in the last decade or so. In 1986, Quirke et al conducted one of the first ever studies on local recurrence based on what they described as the lateral margin, or the LRM. They concluded that the most common cause of local tumour recurrence is the lateral spread of the tumour. In today's terminology, this is known as a positive

circumferential resection margin. They also realized that those with an involved LRM, even if there were no local recurrences, they had distant metastasis , like the liver (25).The Norwegian Rectal Cancer group reported on circumferential resection margins with 29-month median follow-up in 686 patients who had curative intent LAR with TME alone (no adjuvant radiotherapy) for rectal adenocarcinoma. The Norwegian group found that the overall local recurrence rate was 7% (22% with positive CRM and 5% with a negative CRM). 40% of patients with a positive CRM developed distant metastases whereas only 12% of those with negative CRM developed distant disease. (29) In this study a positive CRM clearly affected survival. In another report of 90 patients undergoing resection for rectal cancer, when the radial margins were histologically positive, the hazard ratio (HR) for local recurrence was 12.2, and the hazard ratio for death was 3.2 when compared with those with clear circumferential margins.

According to current definitions, the circumferential resection margin or CRM of a rectal resection specimen corresponds to the the non-peritonealised surface of the rectal resection specimen created by dissection of the sub peritoneal aspect at surgery. It is measured as the shortest distance between the outer margin of the tumour or positive mesorectal lymph node and the surgically resected plane when viewed in a transverse section through the rectum. A distance of less than or equal to 1 mm is accepted as positive CRM.

Achieving a negative CRM is of paramount importance in the surgical management of rectal carcinomas, and this is highly dependant on the operative technique, which has evolved over several years to meet this requirement

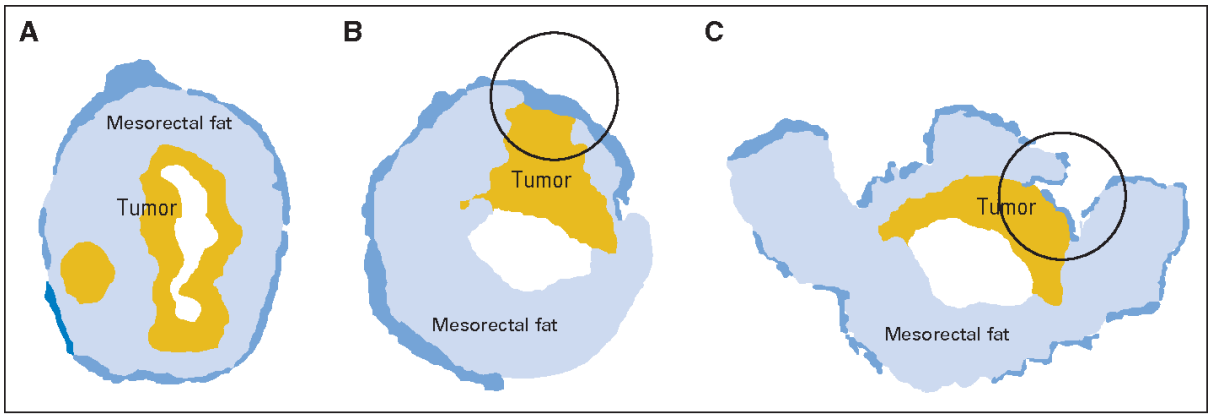

Figure 14: Pictorial representation of CRM

The above figure depicts clearly how a negative CRM appears on the transverse section of a rectal resection specimen. The darker shade of blue indicated the outer margin of resection, and yelloe the tumour. The first picture (A) represents a negative CRM, where both the tumpur as well as the involved node are within the dark blue margin. Figure (B) represents a positive CRM due to the locally advanced tumour directly involving the resection margin. The third figure (C), shows a small tumour with a positive CRM, due to incomplete mesorectal

resection. This type of CRM positivity can be avoided by total mesorectal resection.

3.6.4 TOTAL MESORECTAL EXCISION

Total mesorectal excision or TME is the excision of the tumour en bloc with its blood and lymphatic supply, ie :the mesorectum by means of sharp dissection. It was described by Heald and colleagues in 1982, and is now considered the gold standard for surgical treatment of middle and lower third rectal cancers. The dissection is carried out in an avascular areolar plane between the mesorectum and the parietal fascia. The concept of TME evolved from the principles that originated from observations made by Moynihan in 1908, regarding potential pathways for lymphatic spread. Heald et al hypothesised that the mesorectum represents embryologic advantages conferring protection against tumour dissemination until the terminal stages. The case for TME was made all the more strong by studies which showed improvement in survival with negative CRM.

TME reduces the rate of loco-regional recurrence in rectal cancer by indirectly achieving a negative CRM. Heald et al documented a 0% 2-year local recurrence rate, without adjuvant radiation therapy, in their initial series of 100 cases and an 8% at 10 years among patients who had curative rectal resection. Various studies have shown a local recurrence rate of about 6.5% in TME resections by facilitating a negative CRM, as opposed (27,29) to 14 to 40% in the pre TME.

The Swedish and Dutch trials are the most popular ones that tried to standardise TME resections.

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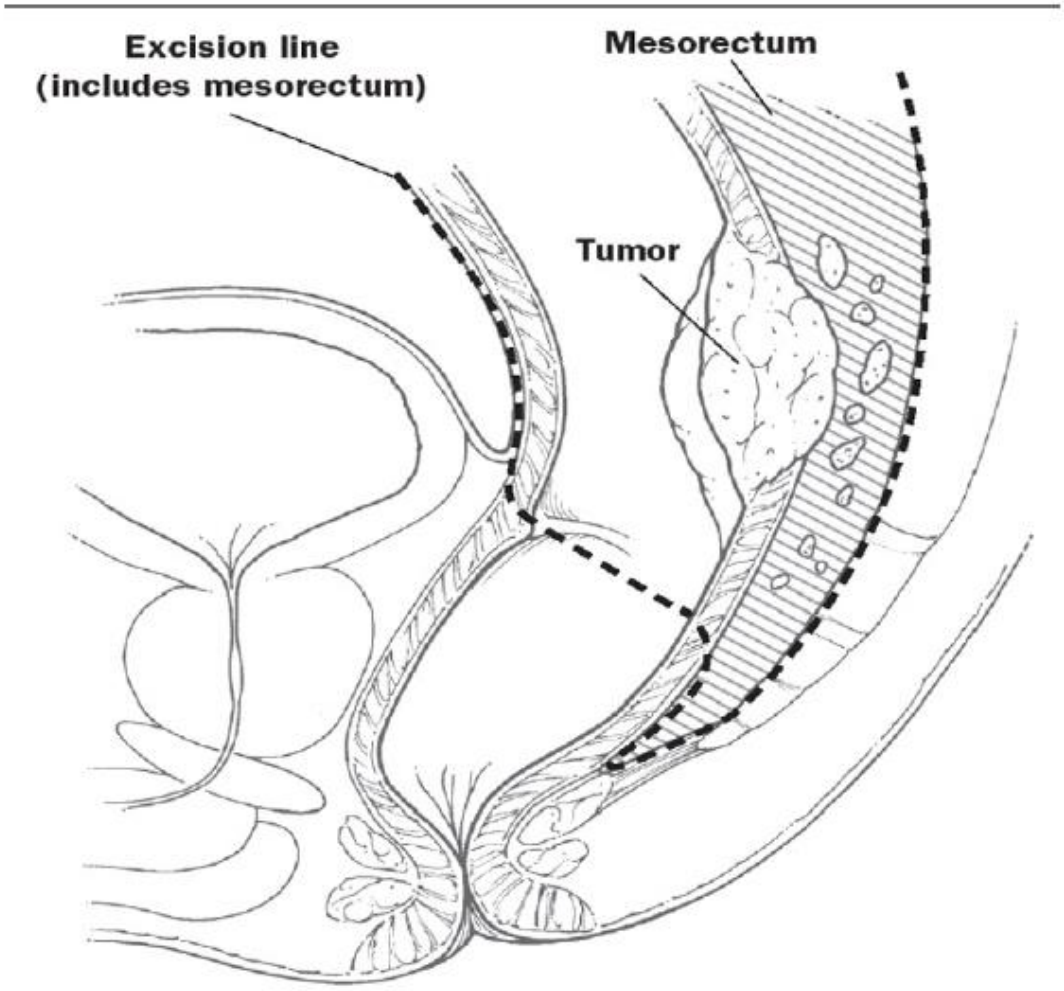


Figure 15: Total Mesorectal Excision

3.6.5 SURGICAL APPROACHES

The surgical approach to rectal resection depends on the site of the tumour in relation to the pelvic floor and the anal spincters. They are broadly divided into sphincter preserving and sphincter sacrificing operations.

Anterior resection

Low anterior resection

Ultra low anterior resection

Abdomino-perineal excision

Extra Levator abdomino-perineal excision

The anterior resections are sphincter preserving operations with are more suitable for high and mid rectal tumours. The abdominal perineal excision is a sphincter sacrificing operation in which the patient will have a permanent end colostomy. There are done for those tumours involving lower rectum and the sphincter complex, where restoring the bowel continuity will lead to incontinence and poor quality of life. The decision on the type of operation is made based on a number of factors including lower margin, relationship of tumour to anal sphincters and pelvic floor, pre treatment staging technical expertise available and patient preference. (26) (27)

With better technology, neo-adjuvant therapy and expertise in the field, more and more sphincter preservation is being practised for lower rectal tumours.

Retrospective studies have shown that even a distal mural margin as small as 1 cm may be oncologically safe. (26) Inter-sphincteric resection with colo-anal hand sewn anastomosis is being practiced in various centres of expertise. The treating surgeon has to maintain a fine balance between oncologically safe margins, function preservation, quality of life and sphincter preservation when it comes to choosing the type of operation.

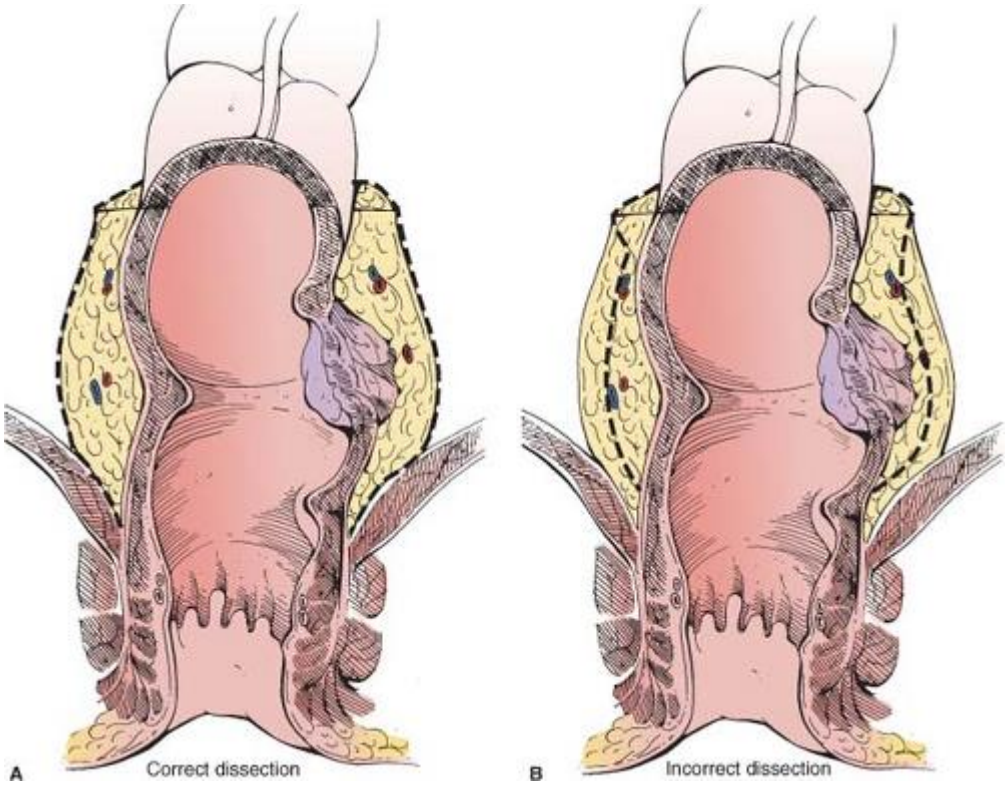


Figure 16: TME resection in Anterior Resection. (A) Cylindrical specimen with correct TME. (B) Incorrect dissection where the TME plane is not maintained.

3.7 FACTORS AFFECTING CIRCUMFERENTIAL RESECTION MARGIN

Various factors have been proposed to affect the circumferential resection margins in rectal cancer. The Dutch trials had demonstrated that preoperative radiation therapy was found to reduce local recurrence. MRI has evolved as the investigation of choice, to demonstrate the morphology of rectal tumours, and are excellent in predicting breach of the mesorectal plane. But in the scenario of neoadjuvant therapy, post radiation changes and fibrosis can often be mistaken for disease and overcall the disease stage. The T stage and N stage of the disease, histological features, sex of the patient position of the tumour in relation to the anal verge and circumferentially, type of operation and surgeon's experience are some of the other factors that were proven by various studies to be significant predictive factors. (5) While some of these factors indicate the aggressiveness of the disease, others indicate the anatomic constrains of achieving clear margins or the need for further expertise in the operating surgeons. Though a number of factors have been proposed in this list only a few have been found to be statistically significant.

4. MATERIALS AND METHODOLOGY

4.1 STUDY SETTING

This study was carried out in department of General Surgery Unit 2(colorectal surgery) in tertiary care centre in South India. Christian medical College, Vellore.

4.2 RESEARCH DESIGN

This was an *observational cohort study, which was prospective in nature*. Those candidates who fit the inclusion criteria in the above mentioned time period will be approached by the Principal investigator for participating in the study, prior to the undergoing the operation.

The purpose of the study is to assess the factors that can predict a positive circumferential resection margin in adenocarcinoma rectum. . The factors being analysed in this study are the ‘T ‘stage and, ‘N ‘stage of the tumour, the distance of the lower margin of the tumour from the anal verge, the position of the tumour as predominantly circumferential, lateral, anterior or posterior, the gender of the patient, the Body Mass Index of the patient, extra mural venous invasion, CRM positivity on MRI and the histology of the tumour.

The outcome that was being studied was the pre operative predictive capacity of the following factors , to determine a positive Circumferential Resection Margin in the final biopsy specimen.

The factor being studied as primary predictor was the T stage of the tumour.

The Secondary outcomes being studied are the predictive capacity of the following factors for a positive CRM.

1. The distance of the lower margin of the tumour from the anal verge as on rigid sigmoidoscopy or digital rectal examination.

2. The location of the tumour as on MRI as predominantly anterior, posterior, lateral or circumferential.

3. The gender of the patient

4. The Body Mass Index of the patient

5. The Extra mural vascular Invasion of the tumour as on the MRI.

6. The shortest distance between the tumour and the mesorectal fascia, as the CRM mentioned on MRI

7. The histology of the tumour as well differentiated, moderately differentiated or poorly differentiated as on the mucosal biopsy study.

4.3 PERIOD OD RECRUITMENT

All consenting patient who are admitted in the unit of colorectal surgery for rectal resection for adenocarcinoma of the rectum between 01 January 2017 to 15th August 2018, and have undergone neo-adjuvant therapy prior to it are recruited for the study.

4.4 RESEARCH POPULATION

All consenting adult patients diagnosed with adenocarcinoma of the rectum, and who had received neo adjuvant therapy in the form of chemotherapy, radiation therapy or both and are planned for rectal resection under Surgery Unit 2 of CMC Vellore, between January 2017and August 2018 were included in the study. Consecutive patients who fit the inclusion criteria were recruited in the said time period. These patients were all biopsy proven to have adenocarcinoma rectum from mucosal biopsies done prior to the operation. There was no control group in this study. Neither was there an exclusion criterion.

4.5 SAMPLE SIZE CALCULATION

In order to calculate a sample size, the principal investigator did a pilot study on retrospective data available in the department. The records of patients with rectal adenocarcinoma, who underwent rectal resection between April 2014 and March 2015, in Colorectal Surgery in CMC Vellore was studied. A total of 68 patients

underwent the above mentioned operations, and of those 15 were found to be CRM positive. It means that 22% of the patients had a positive CRM. This data was used as the basis for calculation of the sample size for this study.

The sample size was calculated as 100 patients using the following method.

Regression Methods – Simple Logistic Regression	
Proportion of disease	0.22
Anticipated odds ratio	2.5
Power (1- Beta) %	80
Alpha (%)	5
1 or 2 sided	2
Required Sample Size	99

Table No 4.5.1

T stage was taken as the primary factor. Sample size was calculated using the CRM positivity rate of 22% for the year 2014 -2015 from the departmental data.

An anticipated odds ratio of 2.5 for higher T stages was taken as an intermediate value from the range found in the OSTRiCh study.(3)

4.6 DATA GATHERING

Once consented, data was gathered using a pro forma designed for the purpose. The required details as mentioned above were obtained from the patient's examination findings, biopsy report which was used for the initial diagnosis, the MRI pelvis done just prior to the operation and finally the pathological specimen's biopsy which was followed up by the principal investigator.

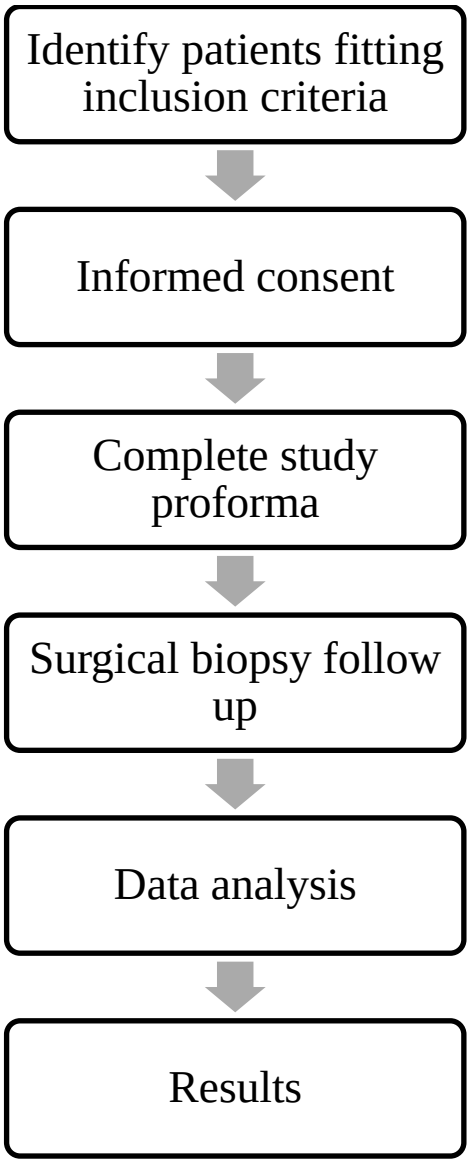
4.7 RESEARCH TOOLS

Data which included the patient demographics, clinical details and relevant investigation results were entered in a pro forma designed for the purpose of this study. The collected data was compiled in a prospectively maintained data base and compiled in EpiData Version 3.1.

4.8 DATA PROCESSING AND STATISTICAL TREATMENT

Once the data was compiled, it was processed using various software including Microsoft Excel 2010 and SPSS v. .The probability of how much each of those factors can predict a positive CRM was calculated from the analysis of the various data collected. The quantitative variables were expressed as frequency tables and bar plots. The proportion was compared among all predictors using Chi square test and Fischer's test. The univariant logistic analysis was used to find the significant predictors. 'p' value and odds ratio was calculated.

5. ALGORITHM OF THE STUDY



6. RESULTS

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The total of 79 histologically proven adenocarcinoma rectum, post neo-adjuvant , and planned for rectal resection were recruited in the study . Of these, two patients were found to be inoperable on table due to intra- abdominal metastasis and one did not have an MRI pre operatively, hence were excluded from the analysis.

6.1 DEMOGRAPHICS

6.1.1 AGE

There was a wide range of age distribution in age from 22 years to 80 years, with a mean of 49.4 years. Most of the patient (48.68%) were in the 40 to 60 years age group. The median age was 51 years and the mode was 43 years.

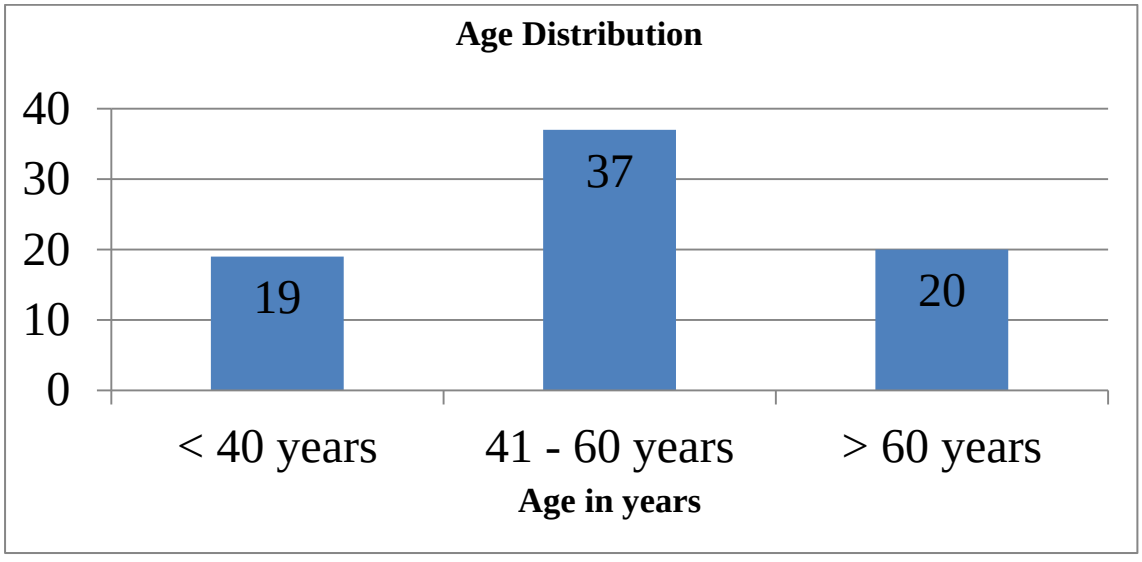

Figure 6.1

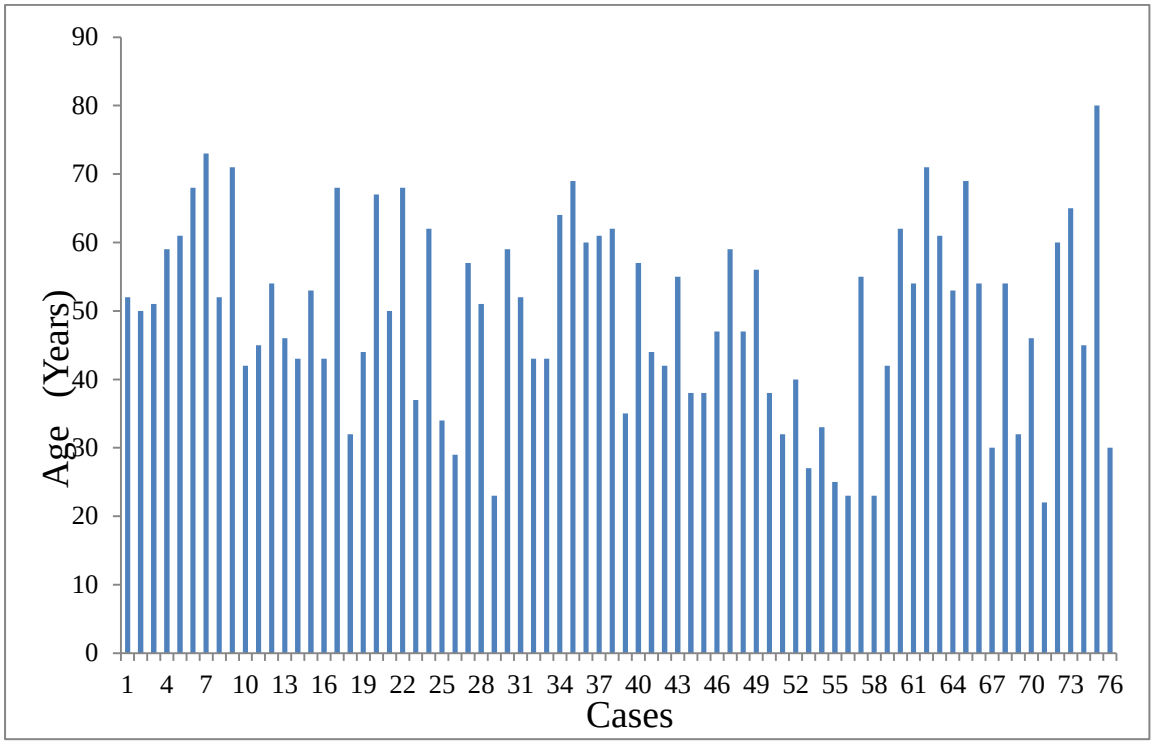

Figure 6.2

6.2 PATIENT FACTORS

6.2.1 SEX

There was a male preponderance with 63.16%, i.e. 48 of the 76 of the cases being male. `Out of the 5 cases with a positive CRM , 4 where female and 1 male

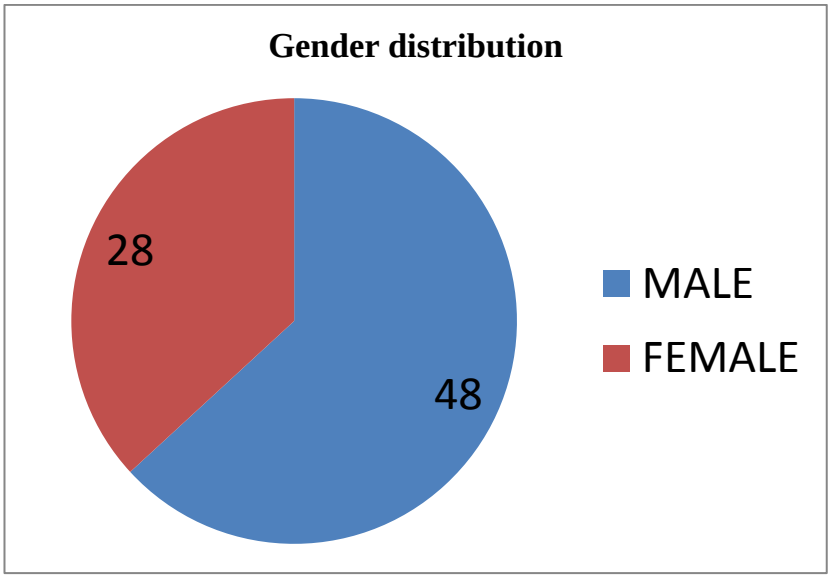

Figure No 6.3

	Male	Female
CRM Positive	1	4
CRM Negative	47	24

Table No 6.1

6.2.2 BODY MASS INDEX

A profile of the body mass index of the patient showed a range between 16Kg/m2 to 32Kg/m2. For ease of analysis, they were classified according to theBMI classification for South Asians.

BMI	Percentage	Frequency
< 18.5	11.8	9
18.5 to 22.9	28.9	22
23 to 24.9	21.1	16
> 25	38.2	19

Table No 6.2

As in the table, very few 11.8% fell into the less than 18.5kg/m2 category. On reclassifying, we found that most of our patients were in the normal to over weight category. Only two patients had BMI more than 30Kg/m2.

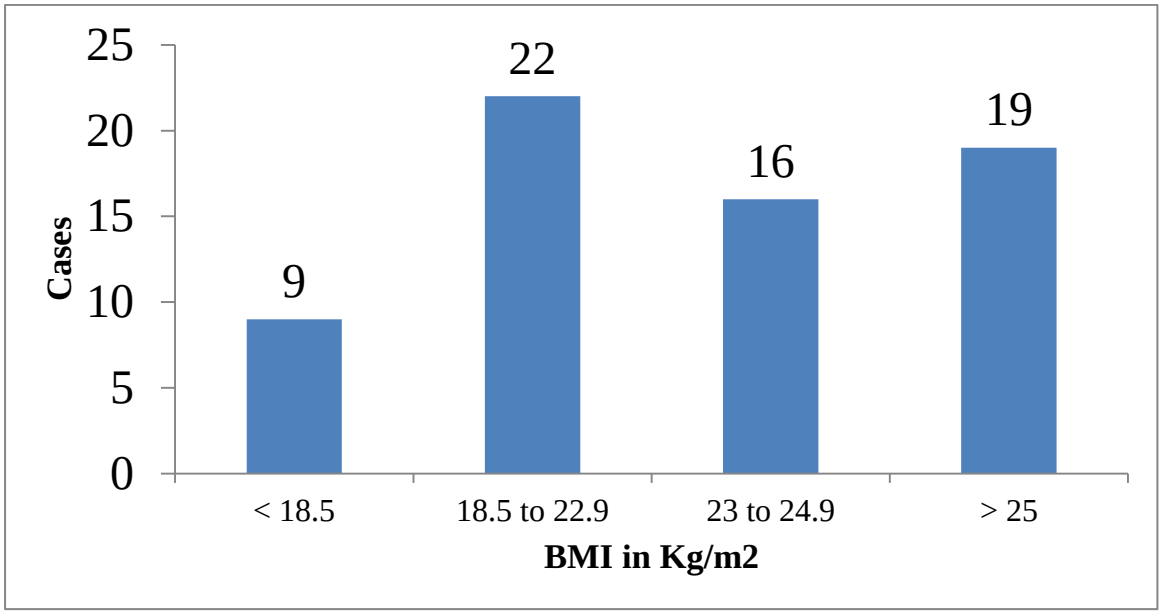

Figure No 6.4

Cross tabulation with the cases with positive CRM did not give any significant results. Both cases with BMI > 30 kg/m2 were CRM negative. On the other end of the spectrum too there were 9 cases with BMI less than 18.5kg/m2 and all of these were also found to be CRM negative. Chi square test did not elicit any significant association between BMI of the patient and CRM positivity.

BMI vs CRM			CRM involvement		Total
			Positive	Negative	
BMI	<18.5	Count	0	9	9
		% within BMI	0.0%	100.0%	100.0%
	18.5 - 22.9	Count	2	20	22
		% within BMI	9.1%	90.9%	100.0%
	23-24.9	Count	1	15	16
		% within BMI	6.3%	93.8%	100.0%
	>=25	Count	2	27	29
		% within BMI	6.9%	93.1%	100.0%
Total		Count	5	71	76
		% within BMI	6.6%	93.4%	100.0%

Table No 6.3

6.3 TUMOUR FACTORS

6.3.1 TUMOUR HISTOLOGY

A majority of the tumours were moderately differentiated, making up 76% of all the cases . Well differentiated was 10.66 % and poorly differentiated was 13.33%. Only 4 out of all these cases had signet ring morphology.

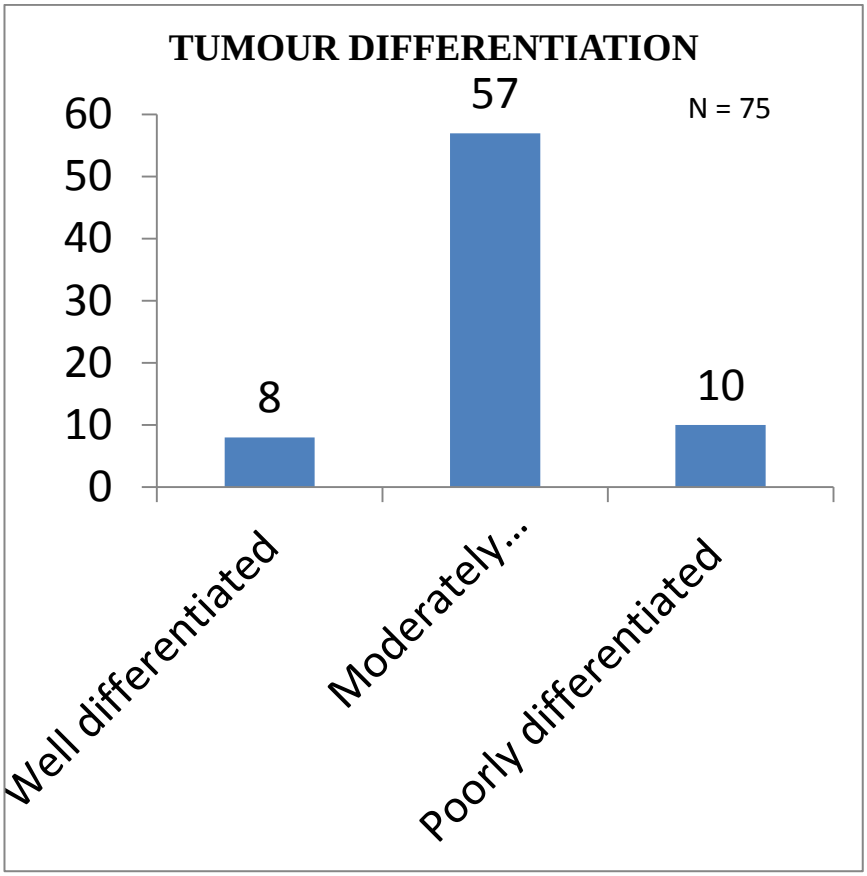

Figure No 6.5

			CRM involvement	
			Positive	Negative
Tumour histology grade	Well Differentiated	Count	0	8
		% within Tumour histology grade	0.0%	100.0%
	Moderately Differentiated	Count	2	55
		% within Tumour histology grade	3.5%	96.5%
	Poorly Differentiated	Count	3	7
		% within Tumour histology grade	30.0%	70.0%
Total		Count	5	70
		% within Tumour histology grade	6.7%	93.3%

Table No 6.4

Tumour histology was compared to CRM positivity and 30% (3/10) of the adenocarcinomas that were poorly differentiated were found to be CRM positive as opposed to 0% in the well differentiated and 3.5 % in the moderately differentiated,

On applying the Pearson Chi- Square test, the P value was 0.006. Hence the grade of differentiation of the tumour was found to be a statistically significant factor in predicting CRM.

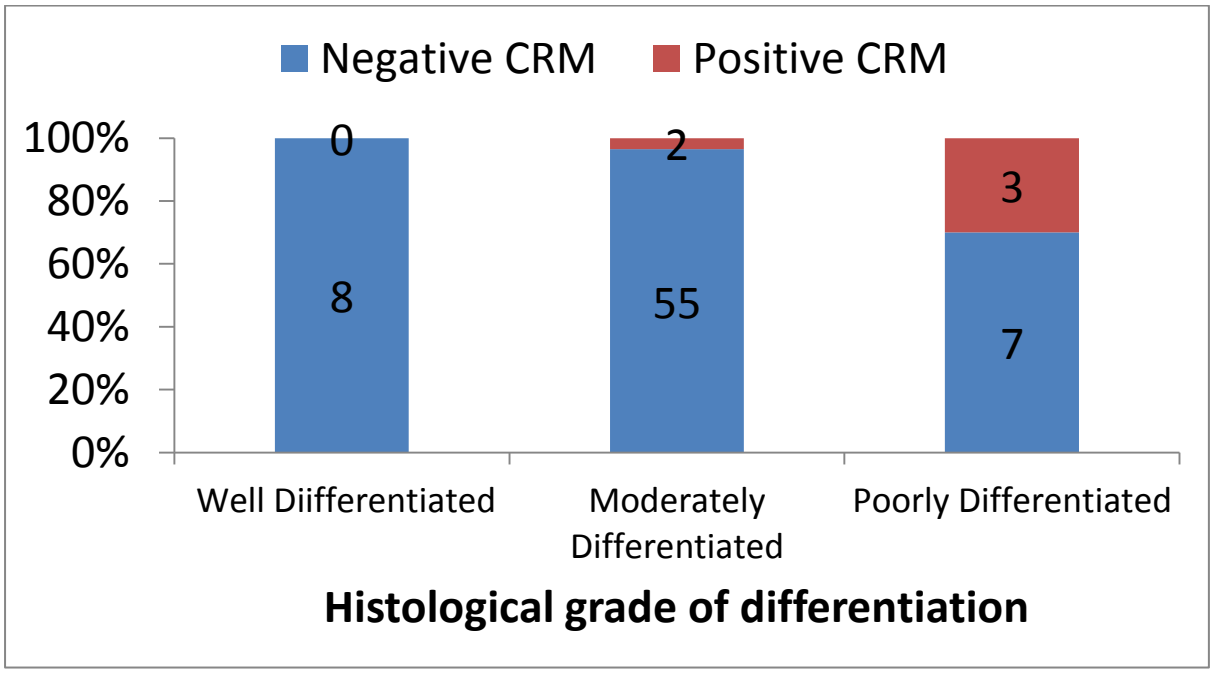

Figure No 6.6

6.3.2 TUMOUR STAGE

The T stage of tumour was determined by the MRI. T0 indicated complete tumour resolution on imaging. Our data did not have any cases with T1 stage

tumours. 50% (38/76) cases were stage T3 while 20% (15/776) were T4. 6 cases had complete radiological resolution (7.9%).

T stage	**Frequency**	**Percentage**
T1	0	0%
T2	17	22.37%
T3	38	50.0%
T4	15	20.0%
T0	6	7.89%

Table No 6.5

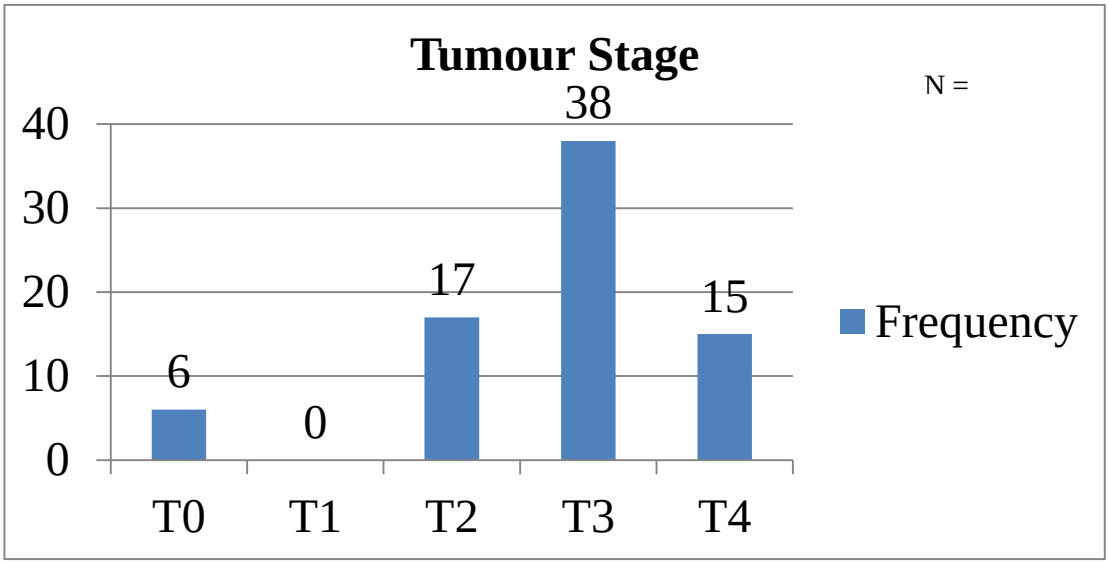

Figure No 6.7

. 20% of T4 tumours were CRM positive, 5.9% of T2 and 2.6% of T3. This is in variance to published data where there is a progressive increase in CRM positivity as the stage of the tumour increases. There was also no significant association between T stage and CRM positivity, with the p = 0.122

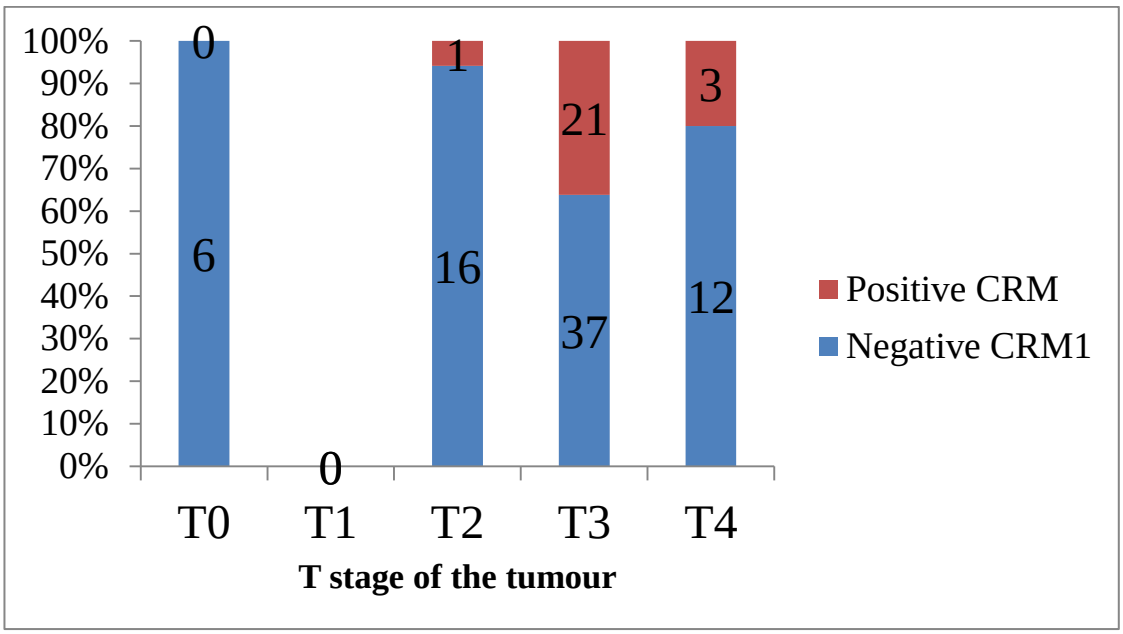

Figure No 6.8

T stage		CRM Involvement		Total
		Positive	Negative	
T0	Count	0	6	6
	% within T stage	0.0%	100.0%	100.0%
T2	Count	1	16	17
	% within T stage	5.9%	94.1%	100.0%
T3	Count	1	37	38
	% within T stage	2.6%	97.4%	100.0%
T4	Count	3	12	15
	% within T stage	20.0%	80.0%	100.0%
Total	Count	5	71	76
	% within T stage	6.6%	93.4%	100.0%

Table No 6.6

6.3.3 NODAL STAGE

The 'N' stage of the disease was also determined as per pre -operative MRI. 42 of our cases were N0 disease making 55.26 % while only 6 (7.89%) were N2. The remaining were N1 disease , 36.8%.

N stage	Frequency	Percentage
N0	42	55.26
N1	28	36.84
N2	6	7.89

(N = 76)

Table No:6.7

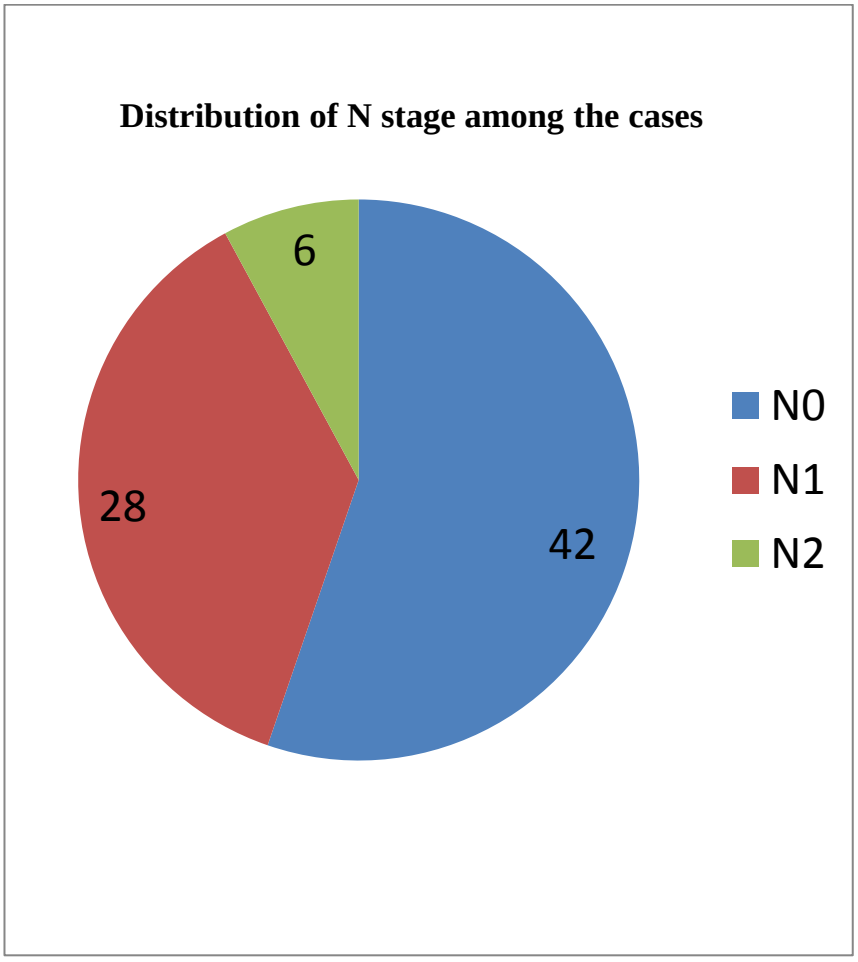

Figure No 6.9

			CRM involvement		
			Positive	Negative	Total
N stage	N0	Count	2	40	42
		% within N stage	4.8%	95.2%	100.0%
	N1	Count	1	27	28
		% within N stage	3.6%	96.4%	100.0%
	N2	Count	2	4	6
		% within N stage	33.3%	66.7%	100.0%
Total		Count	5	71	76
		% within N stage	6.6%	93.4%	100.0%

Table No 6.8

On comparing 'N ' stage with CRM positivity in our group, 60% of the CRM positive cases had nodal disease, with N2 disease making up 33%. On Pearson Chi- Square test , p value was found to be 0.022, hence N stage was found to be a significant factor in predicting CRM positivity.

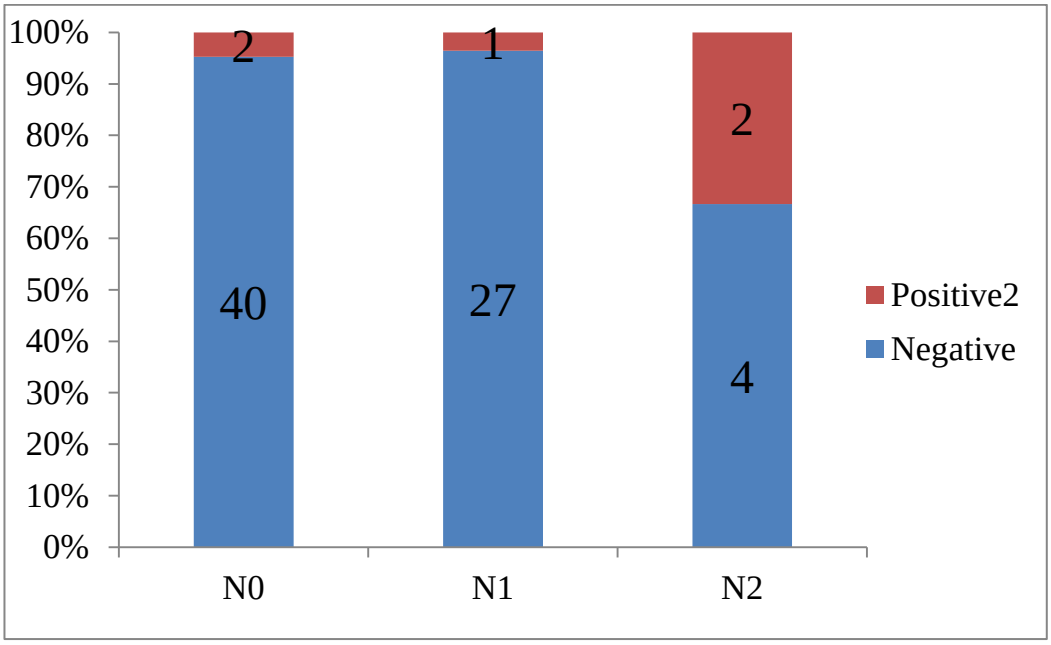

Figure No:6.10

6.3.4 EMVI – EXTRA MURAL VASCULR INVASION

Among the study population the prevalence of EMVI was 18.42 %, making up

14of the 76 cases.

EMVI	Frequency	Percentage
Yes	14	18.42
No	62	81.58

Table No 6.9

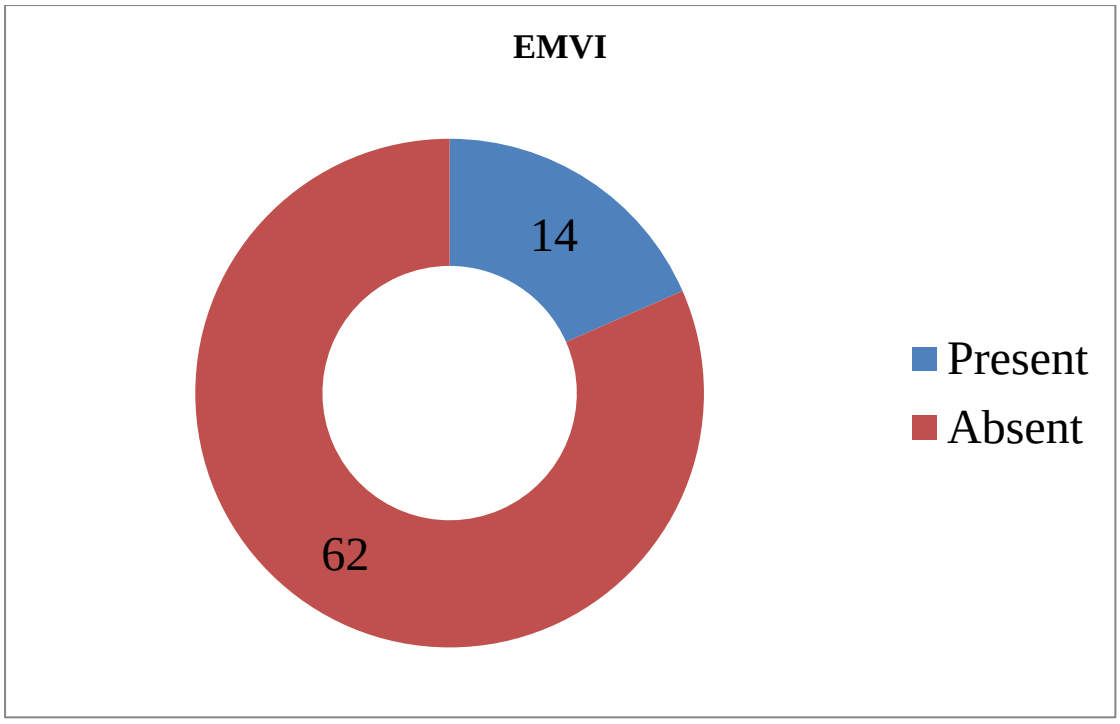

Figure No 6.11

On univariate analysis with those with positive circumferential resection margin, 14% of patients with EMVI had positive CRM, as opposed to 5% in patients who did not have EMVI. This was not statistically significant.

			CRM involvement		
			Positive	Negative	Total
Extra Mural Vascular Invasion	Yes	Count	2	12	14
		% within Extra Mural Vascular Invasion	14.3%	85.7%	100.0%
	No	Count	3	59	62
		% within Extra Mural Vascular Invasion	4.8%	95.2%	100.0%
Total		Count	5	71	76
		% within Extra Mural Vascular Invasion	6.6%	93.4%	100.0%

Table No 6.10

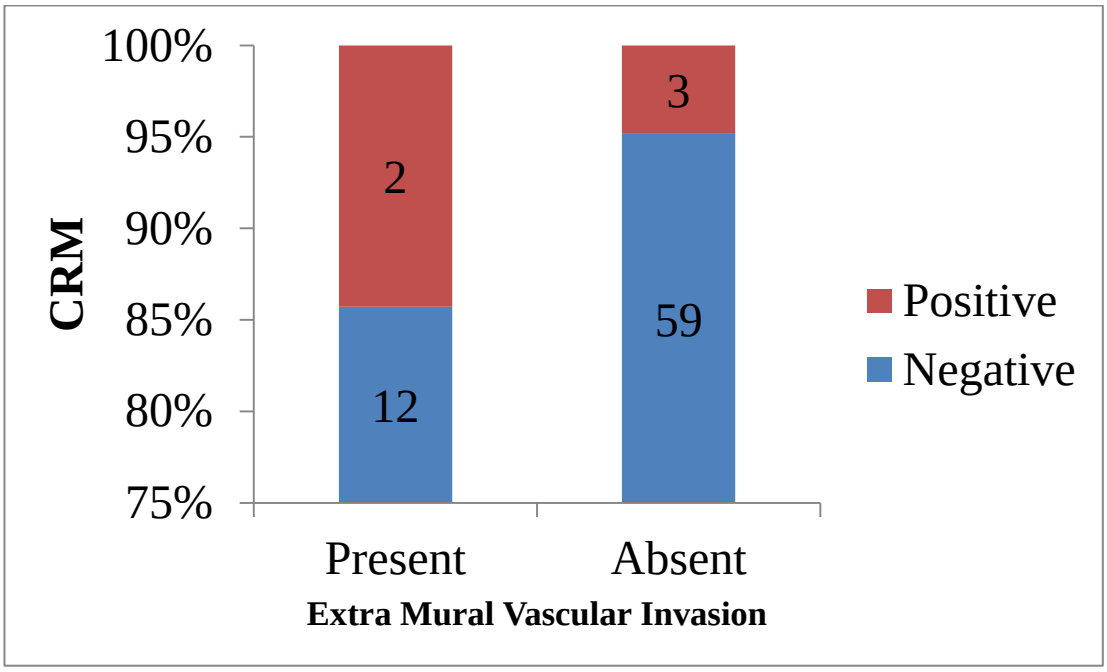

Figure No 6.12

6.3.5 CIRCUMFERENTIAL LOCATION OF THE TUMOUR

The location of the tumour circumferentially in the lumen of the rectum was analysed. We found that out of the 76 cases, 35 had circumferential involvement with 14 anterior, 4 posterior(5%) and 17 as predominantly left or right lateral aspect.

Position	Frequency	Percentage
Anterior	14	18.42
Posterior	4	5.26
Lateral	17	22.37
Circumferential	35	46.52

Table No 6.11

49 of the tumours out of 76 (64.5%) of the tumours had some form of involvement of the anterior aspect of the rectal circumference- with either circumferential involvement or just anterior location. This was also interpreted

based on the preoperative imaging – MRI Pelvis. The final histo-pathological involvement was not looked into.

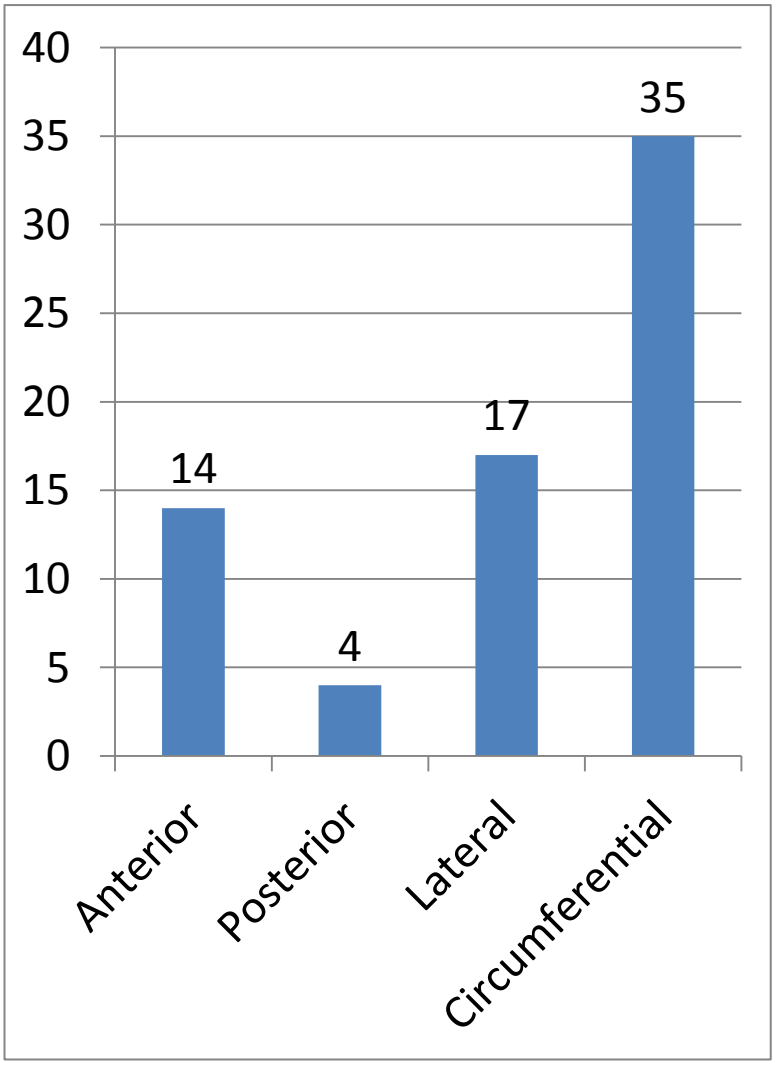

Figure No 6.13

On comparing circumferential position with CRM positivity, none of the posteriorly located tumours were found to have positive CRM. 7.1% of anteriorly located tumours and 8.6% of circumferentially located tumours had

positive CRM. 5.9% of laterally located tumours had positive CRM. This data was not statistically significant.

			CRM involvement	
			Positive	Negative
Circumferential position of tumour	Anterior	Count	1	13
		% within Circumferential position of tumour	7.1%	92.9%
	Posterior	Count	0	4
		% within Circumferential position of tumour	0.0%	100.0%
	Lateral	Count	1	16
		% within Circumferential position of tumour	5.9%	94.1%
	Circumferential	Count	3	32
		% within Circumferential position of tumour	8.6%	91.4%
Total		Count	5	65
		% within Circumferential position of tumour	7.1%	92.9%

Table No 6.12

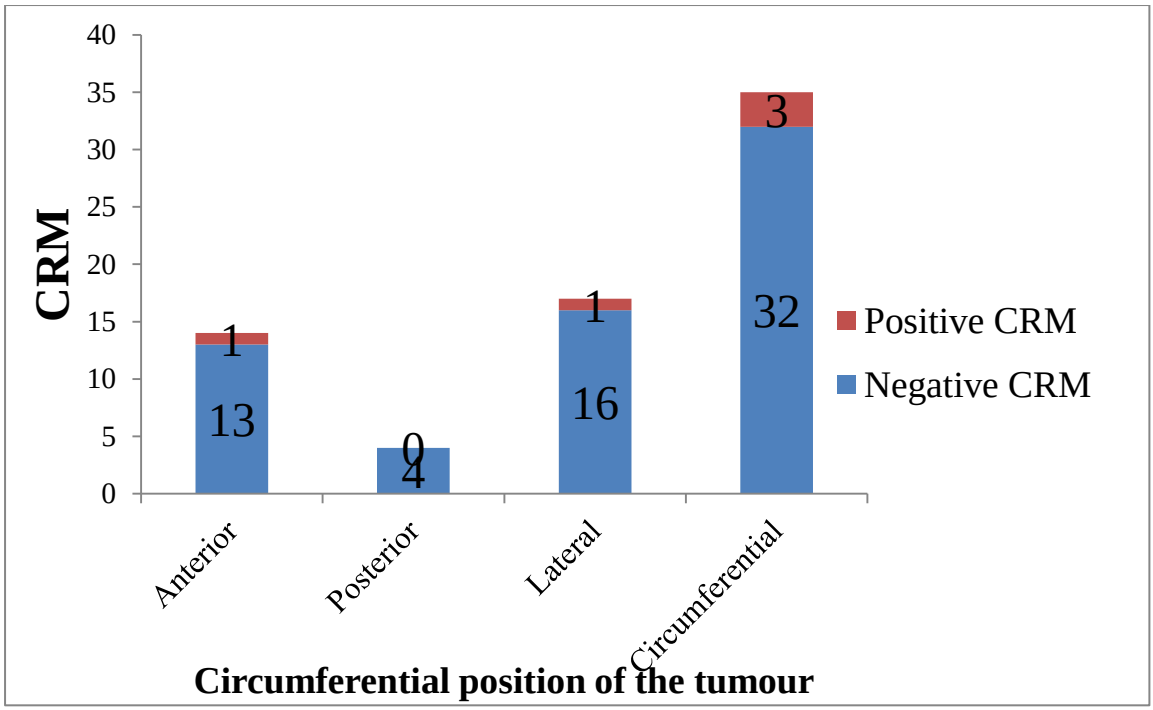

Figure No 6.14

		CRM involvement		Total
		Positive	Negative	
Anterior involvement	Count	4	45	49
	% within	8.2%	91.8%	100.0%
Others	Count	1	20	21
	% within	4.8%	95.2%	100.0%
Total	Count	5	65	70
	% within	7.1%	92.9%	100.0%

Table No 6.13

On comparing the lesion as those with anterior involvement versus CRM, 4 out of 49 (8.2%) had a positive CRM as opposed to 1/20 in the other group with the comparison having a $p > 0.99$, hence not statistically significant

6.3.6 DISTANCE FROM THE ANAL VERGE

The lower most extent of the tumour from the anal verge was taken as the distance of the tumour from the anal verge. They ranged from 1 cm to 14 cm in the group. For ease of analysis they were classified as upper, middle and lower rectal tumours as upto 5 cm , > 5 to 10 cm and > 10 cm .

Distance (cm)	**Frequency**	**Percentage**
Upto 5	27	35.5
>5 to 10	47	61.8
> 10	2	2.6

Table No 6.14

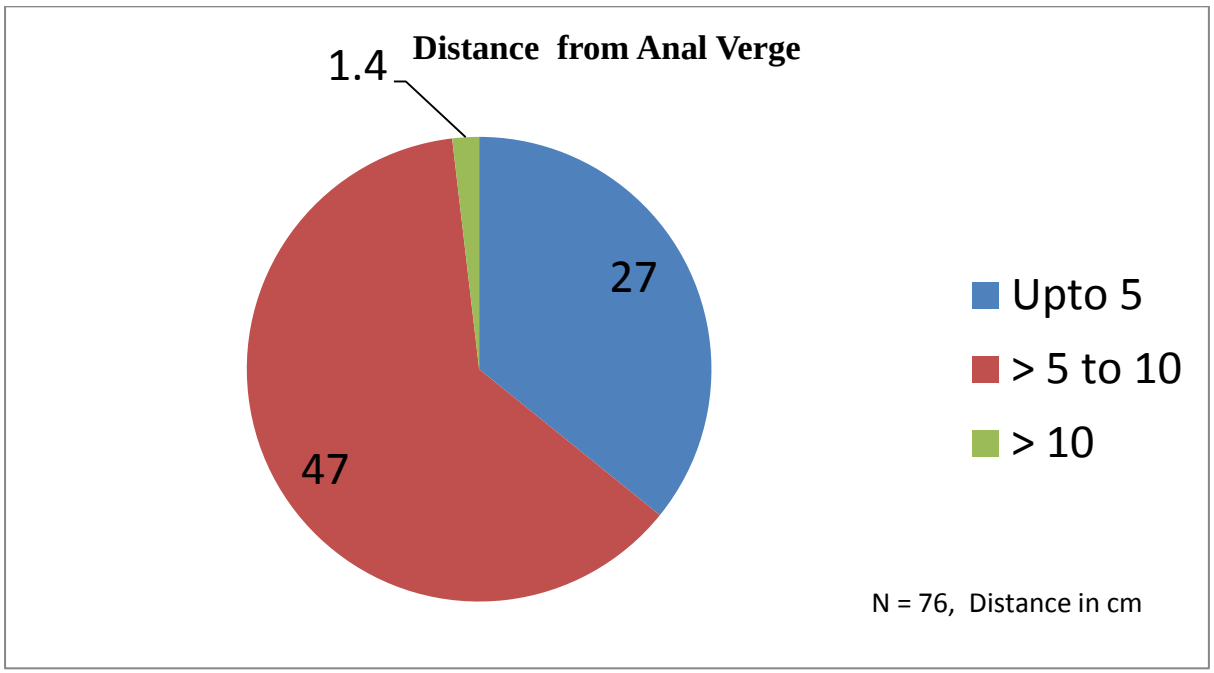

Figure No 6.15

Most of our tumours 61.8% were mid rectal, while 2 were upper and 27(35.5%) were lower rectal tumours. On comparing tumour position with the CRM, 4 of our 5 positive cases were mid rectal, while 1 was lower rectal. None of the upper rectal tumours had positive CRM.

Distance form anal verge			CRM involvement		Total
			Positive	Negative	
D - AV	1-5cm	Count	1	26	27
		% within D- AV	3.7%	96.3%	100.0%
	6-10cm	Count	4	43	47
		% within D- AV	8.5%	91.5%	100.0%
	>10cm	Count	0	2	2
		% within D- AV	0.0%	100.0%	100.0%
Total		Count	5	71	76
		% within D- AV	6.6%	93.4%	100.0%

Table No 6.15

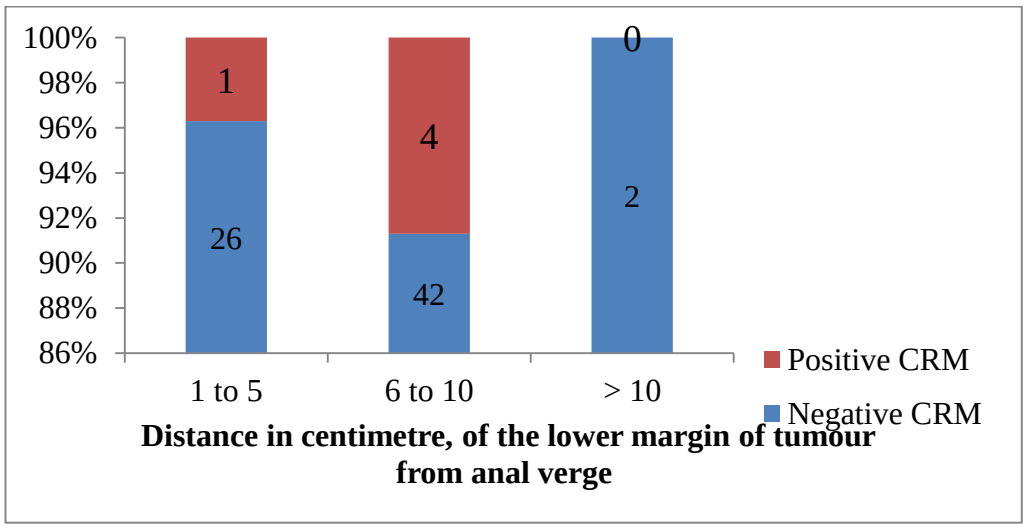

Figure No 6.16

Univariate analysis of the distance of the tumour from anal verge did not yield any significant data though 4/42 cases of mid rectal tumours were CRM positive.

6.4 OPERATIVE FACTORS

6.4.1 TYPE OF OPERATION

Out of the 79 patients 76 had rectal resections.. 44 patients underwent low anterior resection, 3 anterior resections, 11 ultra low anterior resections, 16 abdomino-perineal excisions and 2 extra levator APEs.

Operation type	Frequency	Percentages
AR	3	3.94
LAR	44	57.89
ULAR	11	14.47
APE	16	21.05
ELAPE	2	2.63

Table No 6.16

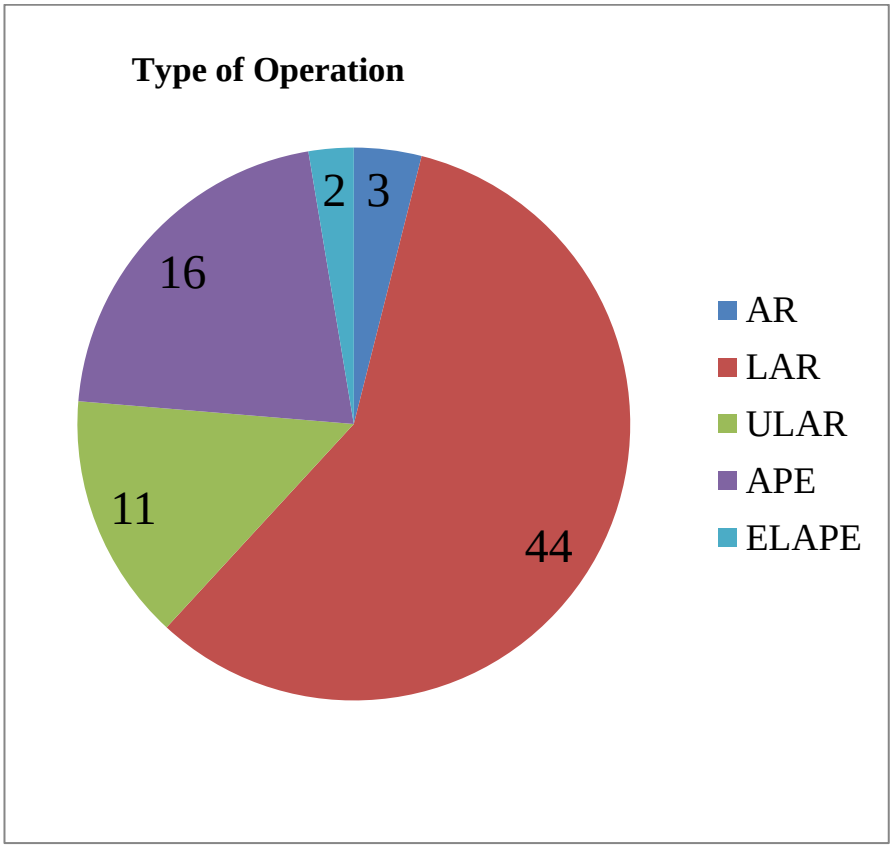

Figure No 6.17

On comparing the type of operation to CRM positivity we found that 4 out of 5 cases of positive CRM had LAR while one had APE. 9.1% of LAR (4/44) and 6.3% (1/15) done had a positive CRM. These associations were not statistically significant.

			CRM involvement		Total
			Positive	Negative	
Type of operation	AR	Count	0	3	3
		% within Type of operation	0.0%	100.0%	100.0%
	LAR	Count	4	40	44
		% within Type of operation	9.1%	90.9%	100.0%
	ULAR	Count	0	11	11
		% within Type of operation	0.0%	100.0%	100.0%
	APE	Count	1	15	16
		% within Type of operation	6.3%	93.8%	100.0%
	ELAP	Count	0	2	2
		% within Type of operation	0.0%	100.0%	100.0%
Total		Count	5	71	76
		% within Type of operation	6.6%	93.4%	100.0%

Table No 6.17

6.4.2 OPERATIVE APPROACH

We analysed the operative approach used in our 76 cases – as in laparoscopic versus open. We had almost equal number of cases in both arms, with a slightly higher number of laparoscopic cases.

Approach	Frequency	Percentage
Laparoscopic	40	53.95
Open	36	46.05

Table No 6.18

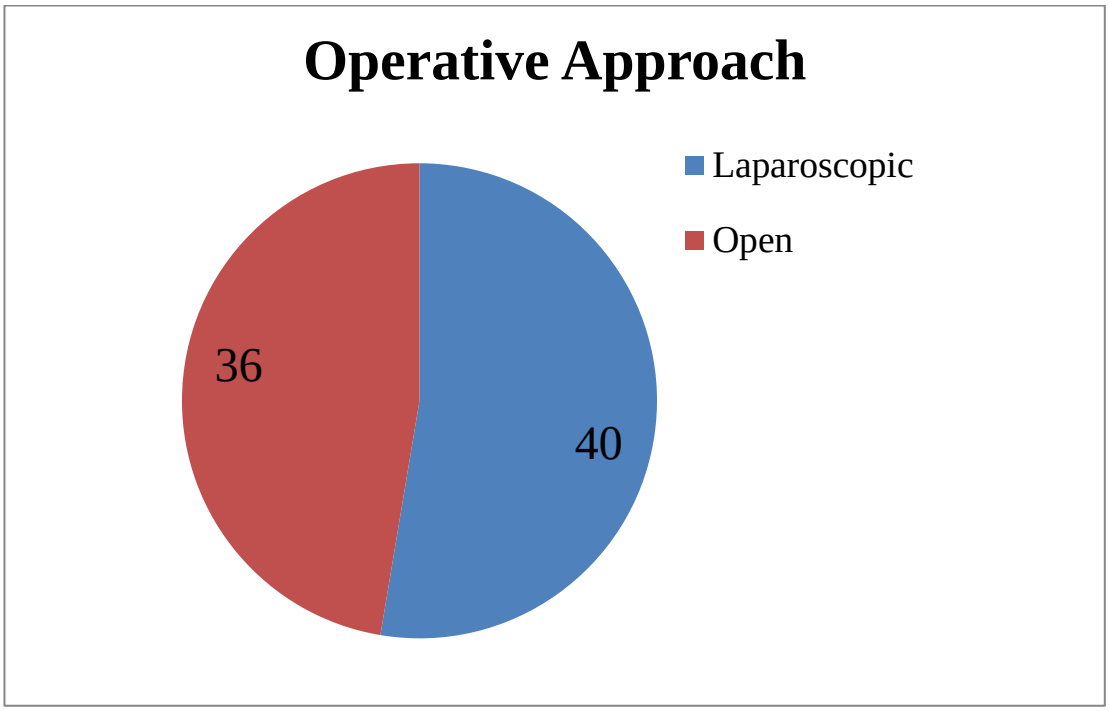

Figure No 6.18

On comparing the type of approach with CRM positivity, we found that 4 out of 36 (11.1%) open cases had positive CRM while only 1 of the 39 laparoscopic cases

(2.5%)had positive CRM. On applying Pearson- Chi square test though, there was no significant co- relation between type of approach and CRM positivity, p = 0.13.

			CRM involvement		Total
			Positive	Negative	
Type of Approach	Laparoscopic	Count	1	39	40
		% within Type of Approach	2.5%	97.5%	100.0%
	Open	Count	4	32	36
		% within Type of Approach	11.1%	88.9%	100.0%
Total		Count	5	71	76
		% within Type of Approach	6.6%	93.4%	100.0%

Table No 6.19

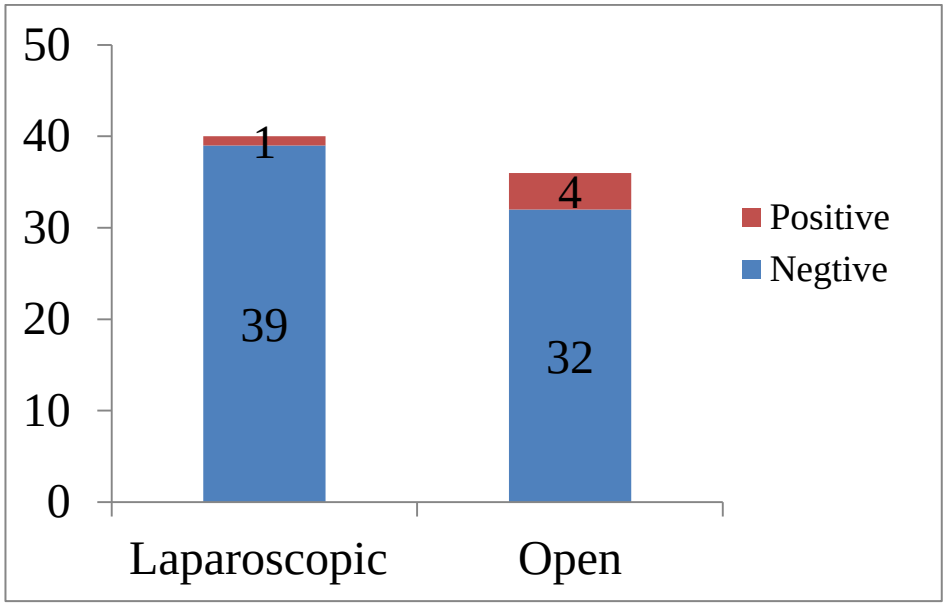

Table No 6.19

6.5 COMPLETE PATHOLOGICAL RESPONSE

Complete pathological response to chemotherapy, with no residual viable tumour on the resection specimen was seen in 22 of the 76 cases, (29 %).

Complete Response	Frequency	Percentage (%)
No	55	72.3
Yes	21	27.6

Table No 6.20

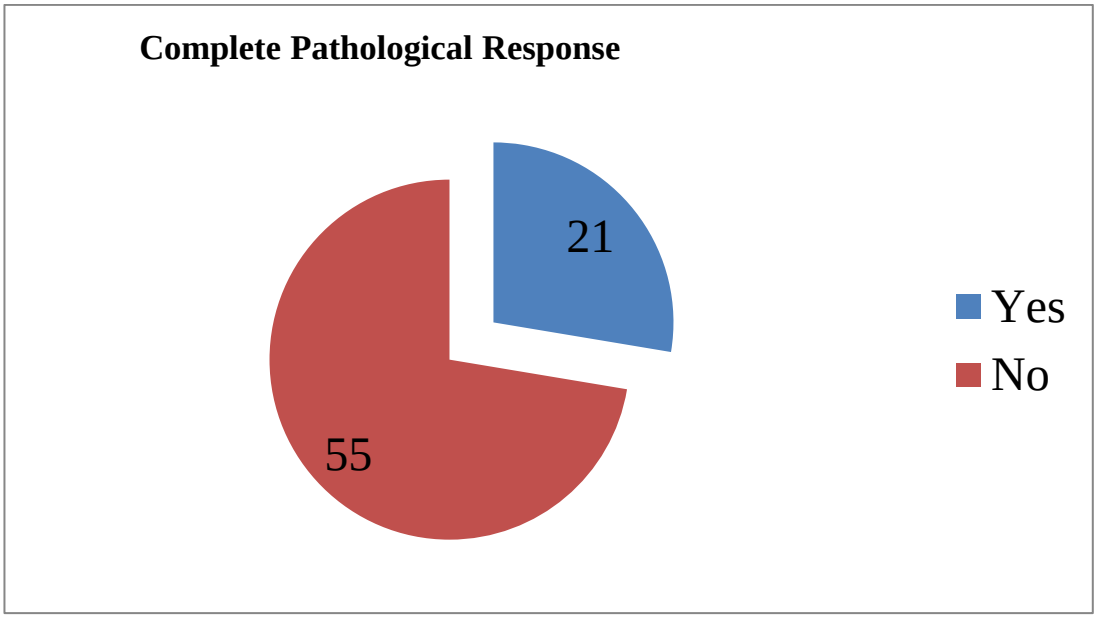

Figure No 6.20

6.6 CIRCUMFERENTIAL RESECTION MARGIN

6.6.1 CRM ON BIOPSY

Our study showed a CRM positivity rate of 6.58% with 5 out of 76 cases having a positive CRM on the biopsy of the resected specimen.

CRM	Frequency	Percentage
Positive	5	6.58%
Negative	71	993.4%

Table No 6.21

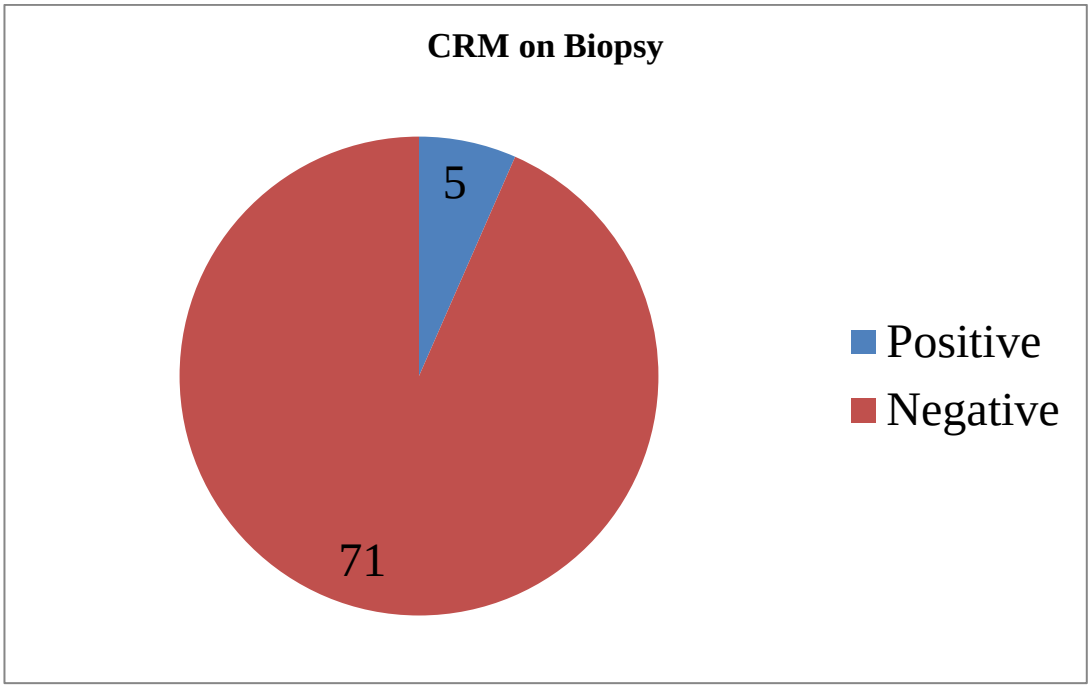

Figure No 6.21

6.6.2 MESORECTAL MARGIN OR CRM ON BIOPSY

Our primary imaging tool of pre- operative assessment was MRI. On the MRI that was taken after the said waiting period after neo- adjuvant therapy, 42 cases out of 76 (55.3%) had a breach of the mesorectal fascia and were reported as CRM positive.

CRM on MRI	Frequency	Percentage
Positive	42	55.3
Negative	28	36.8
No residual tumour	6	7.9

Table No 6.22

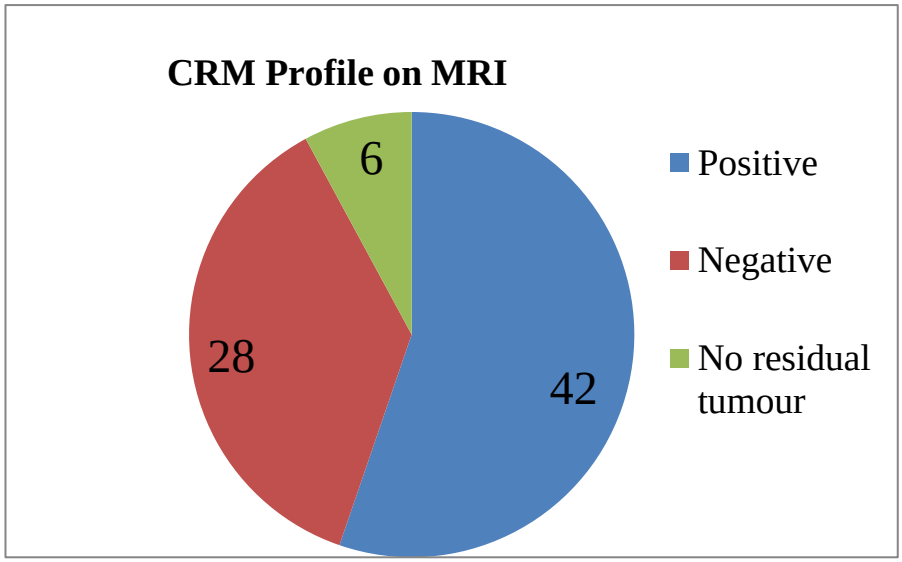

Figure No 6.22

On comparing the CRM on MRI versus the CRM on biopsy, There was significant degree of overestimation by the MRI.

		CRM - MRI			Total
		<=1mm, pos	>1mm, neg	missing, no residual tumor	
CRM - Biopsy	<=1mm, pos	5	0	0	5
	>1mm, neg	28	21	1	50
	missing, no residual tumor	9	7	5	21
Total		42	28	6	76

Table No 6.23

The scatter plot below depicts the significant difference between the MRI and the final biopsy. Those cases which have a positive CRM on the MRI are much larger in number than those on MRI. On testing the sensitivity and specificity of the MRI in picking up CRM positivity, versus the gold standard biopsy, we found the following:

	Outcome +	Outcome -	Total
Test +	5	0	5
Test -	28	21	49
Total	33	21	54

Table No 6.24

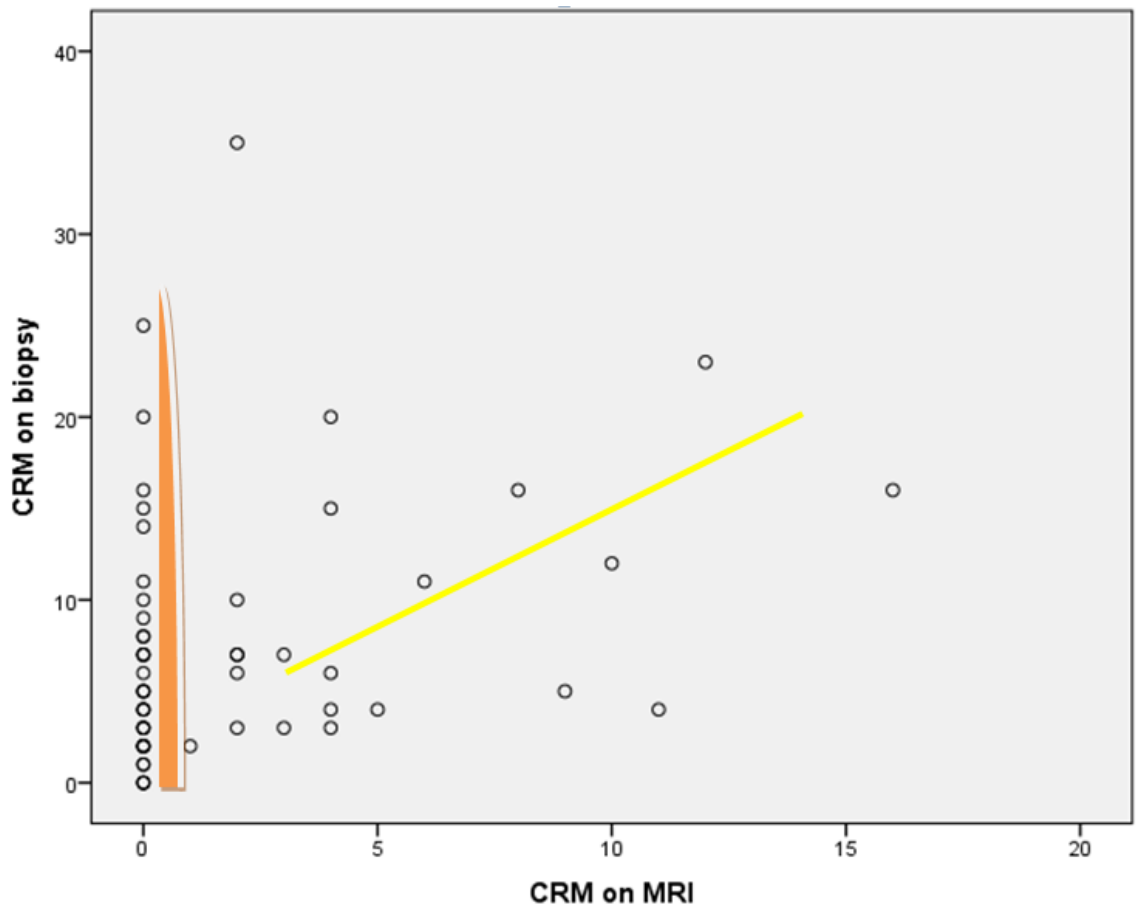

Figure No 6.23

While the sensitivity of the MRI in picking up CRM positive cases was 100%, the specificity was only 15%.

7. DISCUSSION

The demographic pattern seen in our patients, were quite different from that seen internationally. 49% of our cases were between 40 to 60 years of age, which was lower than that seen in the rest of the world – more than 60 years. The rest of the cases were almost equally distributed in the less than 40 and greater than 60 groups. This could be an indication of the changing age profile of patients with rectal malignancy world over, with more and more young patients being identified with the disease. It could also indicate referral bias as the study was done in a tertiary care high volume centre. (1,28)

Majority of our cases were male, and this was in keeping with international statistics. CRM positivity too is more in men, owing to the narrow pelvis, but in our data 80% of our CRM positive cases were women, a statistically significant number. As the total number of patients with a positive CRM were only 5, though statistically significant, we do not think that this data has much clinical relevance. In terms of available literature too, though it has been postulated that CRM positivity should be lower in female patients, data of statistical significance is not available. (3)

There was no real significant corelation between CRM positivity and BMI of the patient. This association was considered, taking into account that, the higher the BMI the greater the mesorectal fat, thus facilitating a greater CRM for resection – hence hypothesising that obesity was a protective factor from positive CRM.

The extrapolation that the converse – thinner people had a higher risk of positive CRM could also not be seen in our data, with all 9 of the less than 18.5 kg/ m2 category having negative CRM. Only 2 patients were > 30k/m2 , and both were found to have a negative CRM, but the Pearson chi square test for this correlation was negative.

Majority of our cases were moderately differentiated. Among our cases, the poorly differentiated tumours had the highest chance being CRM positive. This could be a reflection of the aggressive nature of these tumours. Studies done of larger cohorts also concur that poorer the differentiation, higher the chances of CRM positivity.(3)

On comparing the T stage of the tumour as per the post neo adjuvant MRI versus the CRM on biopsy, it was not found to be a significant contributory factor to CRM positivity. This is not in concordance with most international studies and data where T stage pays a significant role. Another noteworthy point is that despite having 20% of T4 cases, the treating team has gone ahead with rectal resection alone, indicating that the accuracy of the MRI is questionable in staging the tumour and hence the decision. The MRI in most instances tends to overestimate the tumour, especially in a post neo-adjuvant radiotherapy scenario, with difficulty in differentiating between viable tumour and post radiotherapy changes. This has been taken into consideration when opting for operative management in these cases.(29,30)

Lymph node positivity of the disease was found to be a significant factor for determining CRM positivity, with a p value of 0.022. Node positivity in itself has proven adverse prognosis, especially of local recurrence(7), and also for positive circumferential margin in large trials. (6)

EMVI or extra mural vascular space invasion is considered an important determinant of tumour of tumour aggressiveness and risk of systemic failure. 14% of our cases with EMVI had a positive CRM. Though this was not statistically significant, the trend indicted that those tumours with EMVI had a higher chancer of having a positive CRM. Studies elsewhere have shown it to indicate towards nodal disease as well as parietal involvement. The accuracy of EMVI reporting is dependent on the quality and resolution of the MR imaging which may not always be available. (7)(31)

The location of the tumour with respect to the circumference of the rectum is important because of the difference in the surrounding structures and the thickness of the mesorectum. The mesorectum is thinnest anteriorly and thickest posteriorly, hence by extension, tumours that have involvement of the anterior aspect of the rectal circumference have a higher chance of breaching it – leading to a positive CRM. In our study too as like many international ones, we found this to be true. 4 of the 5 tumours with positive CRM had anterior involvement, though there numbers were not statistically significant ($p > 0.99$).

With respect to position of tumour from the anal verge, the lower the site of the tumour, higher is the expected rate of CRM positivity owing to the anatomy of

the rectum. The same has been demonstrated in previous studies. (32) Our study sample did not show a similar trend, with maximum positives in mid rectal tumours. This could again be attributed to the low sample size and also that we had very few upper rectal tumours in our study population, owing to the changing practice of upfront operation in this subgroup.

Traditionally APE is known to have higher CRM positivity. But in our data, all the cases with CRM involvement were sphincter saving operations. One needs to further analyse whether any of these would, under more conventional settings, have been non sphincter saving operations. In view of availability of better stapling techniques and with more advanced skills, those tumours that would have needed sphincter sacrificing operations are undergoing more and more sphincter preserving resections. This could be an indication that we may be compromising oncological safety for bowel continuity. One needs to critically look at larger data set to come to conclusions though.

We compared the type of operative approach with CRM positivity, to look at associations. We found that more of our open operations were CRM positive. (not statistically significant, with $p = 0.13$) . This could be bias due to the technical difficulty of the case or level of experience of the surgeon as open operations were mostly done by trainees as opposed to laparoscopic ones which were done by consultants. Internationally though, most data points to comparable safety of both the approaches. (33) (34)

The CRM positivity rate found in our study was 6.6%, well within the acceptable range internationally. The international rates of CRM positivity range from as low as 3.6% to as high as 17.2% in various studies. (3,35) What was interesting to note was that the co relation between MRI and final biopsy on CRM was poor. The MRI was a sensitive tool but the specificity in our study was as low as 15%. This is because it is often difficult to differentiate between viable tumour, and post chemoradiation changes, resulting in a high degree of false positives. (30) But as depicted on the scatter plot, if one were to exclude all the cases with positive CRM from the comparison, the MRI and biopsy CRMs seem to correlate well.

7.1 LIMITATIONS

The study had several limitations, the most important being the small numbers. Most of the international studies are either multi centre or spanning several years in a single referral institute. Secondly despite there being formats and guidelines for reporting, it was noted that there was significant difference in the manner of reporting both MRIs and biopsies from person to person. Thirdly, the study being done in a teaching setup, there was variation in the surgical technique and expertise in each case, ranging from surgical trainee to Professor, hence case selection would have been biased to begin with. Though the cohort was a post neo-adjuvant chemoradiation subgroup, some received short course therapy while most received long course. This aspect was not looked into in the data analysis.

8. CONCLUSION

The study was an assessment of the various factors predicting a positive circumferential resection margin in adenocarcinoma rectum, post neo-adjuvant chemoradiation. Despite its various limitations, we found that our study also agrees with what much of the published material on the topic has shown previously.

There was significant association between positive Circumferential Resection Margin, nodal staging and histological differentiation of the tumour.

Presence of EMVI, Anterior location of the tumour and BMI < 30 kg/m2 also showed a trend towards greater risk of a positive CRM though the association was not statistically significant.

The lack of co relation of the other data could be attributed to low sample size and referral bias we see, being a high volume colorectal referral center in South East Asia.

We can conclude that those patients with higher nodal stage, poor differentiation, anterior involvement, and EMVI are at higher risk of having a positive CRM. A higher BMI appears to have a protective effect.

More extensive large volume studies would help in coming to substantial conclusions and may even help in creating a risk stratification system. At the moment though, while keeping in mind all the available data, the treating team

needs to take an informed decision regarding the operation to be offered to each individual, in liaison with them.

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9. BIBLIOGRAPHY

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10. ANNEXURE- I

PATIENT INFORMATION SHEET

Study Title: Assessment of factors that predict a positive Circumferential Resection Margin pre-operatively, in rectal adenocarcinoma.

Purpose of research:

This is a study on cancer of the rectum (the last part of the intestine). In this research project, we are trying to study the different factors that can cause a recurrence of rectal cancer after an operation to remove the rectum. By trying to predict it before the operation, we are hoping that the type of operation can be changed to a more suitable one. By doing so we believe that we can reduce the chances of a tumour recurrence , thus improving the life expectancy of such patients.

Expected Duration of the Subject's Participation:

Your participation will be limited to giving consent for accessing your medical records for this study purpose.

Description of the procedure:

After obtaining consent, the chief investigator will note down information regarding your biopsies and MRI scans in special forms. At the end of the process, the data obtained will be analysed.

Risks or benefits to the subject:

By participating in this study, you are not expected to have any risks or benefits. The study is purely observational, which means that participating in the study will not affect the course of your treatment.

Benefit to others:

We are hoping that the results of this study will help us to improve the treatment of adenocarcinoma rectum, by prognosticating better and offer more extensive resections to appropriate patients, thus preventing local recurrence.

Participation:

It is up to you to decide whether to take part or not. You are still free to withdraw from the study at any time, without giving any reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you receive.

Contact Details

Dr : , Ph

11. ANNEXURE II

INFORMED CONSENT

Study Title: Assessment of factors that predict a positive Circumferential Resection Margin pre-operatively in rectal adenocarcinoma.

Study Number: _____

Subject's Initials: _____

Subject's Name: _____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the ***investigators of this study,*** the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

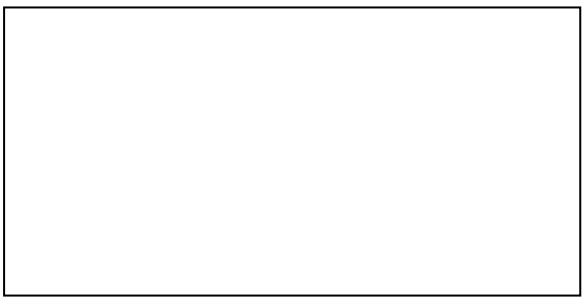
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

_____

12. ANNEXURE III - PROFORMA

ASSESMENT OF FACTORS PREDICTING A POSITIVE CIRCUMFERENTIAL MARGIN IN RECTAL ADENOCARCINOMA

STUDY PROFORMA

DEMOGRAPHIC DETAILS

1. Study Number □□□

2. Hospital Number □□□□□□□

PATIENT FACTORS

1. Age □□

2. Sex 1 Male 2 Female □

3. BMI □□.□□ Kg/m2

TUMOUR RELATED FACTORS

1. Distance from anal verge -------- cm in terms of length

2. Tumour histology grade

    1)Well differentiated □

2) Moderately differentiated

3) Poorly differentiated

3. Signet Ring cells

1) Present □

2) Absent

4. Tumour stage

1) T1

2) T2

3) T3 □

4) T4

5. Nodal stage

1) N0

2) N1 □

3) N2

4. Vascular invasion EMVI

1) Yes □

2) No

7. Circumferential position of the tumour

1) Anterior

2) Posterior □

3) Lateral

4)Circumferential

8. CRM on MRI ……..(in mm)

OPERATION RELATED FACTORS

1. Type of Operation

1) AR

2) LAR

3) ULAR □

4) APE

5) ELAPE

2. Type of approach

1) Laparoscopic □

2) Open

CRM as per the surgical resection specimen ---------- mm

1. Positive (< 1 mm) □ Biopsy Number( )

2. Negative (> 1 mm)

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13. ANNEXURE IV -DATA

hnum	date	age	sex	bmi	dav	hg	sgc	t	n	emvi
663174g	########	52	1	24.2	1	2	2	3	2	
637760g	########	50	2	26.1	2	2	2	5	1	
648071g	########	51	2	19	2	3	2	4	3	
521308g	########	59	2	27.6		2	2	5	1	
498057g	########	61	1	18.3	9	2	2	4	2	
691536g	########	68	1	25.8	8	1	2	2	1	
407896d	########	73	1	18.9	6	2	2	3	1	
707911g	########	52	1	19.9	2	2	2	3	2	
279347c	########	71	2	28	7	2	2	4	3	
725220g	########	42	1	15.5	13	2	2	5	1	
608795f	########	45	2	26.3	6	2	2	4	2	
745640g	########	54	1	27.5	8	1	2	2	1	
685506g	########	46	2	24.4	7	2	2	3	1	
756260g	########	43	1	20.3	8	2	2	2	1	
756069g	########	53	2	20.6	6	1	2	3	1	
752866g	########	43	1	18.4	3	2	2	2	1	
442517f	########	68	1	20.2	8	2	2	3	1	
697893g	########	35	1	20.8	10	1	2	4	1	
185052f	########	63	1	22.7	4	2	2	2	1	
764992g	########	32	1	18.7	13	2	2	4	1	
782789g	########	44	1	18.4	5	2	2	3	3	
261435f	########	67	1	27.7	7	2	2	2	2	
751951g	########	50	1	32	7	2	2	3	2	
811092g	########	68	1	27.4	7	3	1	2	2	
974116b	########	37	1	27.4	3	2	2	3	2	
875997g	########	62	1	21.9	7	2	2	3	1	
879747g	########	34	2	30.6	7	2	2	2	1	
018235h	########	29	2	19.1	2	3	1	4	2	
167887h		57	1	26.9	4	2	2	3	2	
119179h	########	51	1	21.5	10	2	2	3	1	
075539h		23	2	29.1	5	3	2	3	2	
149202h		59	1	23.7	6	2	2	2	1	
109404h	########	52	2	26.6		2	2	3	1	
807487g		43	1	26	4	2	2	3	1	
916114g	########	43	1	23.2	1	2	2	3	1	
903086g		64	1	23	6	2	2	3	2	
890883g	########	69	1	23.4	8	3	1	3	1	
863479g		60	2	22	3	2	2	2	1	
832088g	########	61	1	20.7	10	2	2	3	2	

397404g		62	2	26.1	3	2	2	3	3
355490g	########	35	2	26.6	7	3	2	2	2
906049g	########	57	1	24.9	6	2	2	3	2
873436g		44	2	16	3	2	2	3	2
719214g		42	1	23.1	14	2	2	3	1
985043g		55	2	24.7	10	1	2	2	1
964227g		38	1	23		2	2	3	1
047921h	########	38	2	27.7	4	1	2	3	1
002562h	########	47	1	28.4	9	2	2	3	1
899266g	########	59	1	21.8	4	2	2	2	1
822872g		47	2	21.6	7	2	2	4	1
985553g	########	56	1	21.3	6	2	2	3	1
867023g	########	38	2	18.9	7	2	2	4	2
966885g		32	1	25.7			2	3	2
917391g	########	40	2	18.1		1	2	2	1
871803g		27	2	25.3	6	3	1	4	3
970462g		33	2	28.7	8	2	2	4	3
961469g	########	25	2	23.3	4	2	2	3	2
086842h		23	1	20.1		1	2	2	1
948151g	########	55	1	20.7	4	2	2	2	1
012240h	########	23	2	17.2	7	3	2	4	2
988573g	########	42	1	27.1	7	3	2	3	1
142888h		62	1	19.8	6	2	2	3	2
094720h	########	54	1	19.68	8	2	2	2	1
095681h	########	71	1	23.3	6	1	2	3	2
938987g		61	1	23.6		2	2	3	1
706128g		53	1	24.7	8	2	2	4	2
724182g		69	1	19.6	9	2	2	4	2
794498g		54	2	28.1	7	2	2	3	2
851269g		30	1	27.1	5	2	2	4	1
262888f		54	1	26.4	4	2	2	5	1
869958g		32	1	26	7	3	2	3	2
557298g		46	2	17	8	2	2	2	1
936175g		37	1	23	13	3	2		
966073g		22	2	17.3		2	2	3	2
878559c		60	2	27	8	2	2	4	1
989229g		65	1	23	3	2	2	3	1
901767g		45	1	24.3	5	2	2	5	1
942605g		80	1	25.4	7	2	2	3	2
723985g		30	1	18.6		2	2	5	1

cpt	cr	crmi	oper	to	ta	crmb	crm
4	FALSE	0	TRUE	4	2	3	2

	TRUE		TRUE	4	1		2
3	FALSE	0	TRUE	4	2	0	1
	TRUE		TRUE	2	1	6	2
4	FALSE	3	TRUE	2	2	7	2
2	FALSE	16	TRUE	2	1	16	2
1	FALSE	4	TRUE	2	2	20	2
4	FALSE	3	TRUE	4	1	3	2
4	FALSE	0	TRUE	2	1	0	1
	TRUE	3	TRUE	2	2		2
1	FALSE	4	TRUE	3	1	6	2
4	TRUE	3	TRUE	2	1		2
3	FALSE	5	TRUE	2	1	4	2
1	FALSE	0	TRUE	2	2	6	2
4	TRUE	0	TRUE	2	2		2
1	TRUE	3	TRUE	3	1		2
3	FALSE	0	TRUE	2	1	25	2
4	FALSE	0	FALSE				
4	FALSE	0	FALSE				
4	FALSE	1	TRUE	2	2	2	2
4	FALSE	0	TRUE	2	2	0	1
3	FALSE	10	TRUE	2	2	12	2
4	FALSE	4	TRUE	2	1	15	2
1	FALSE	6	TRUE	2	1	11	2
4	FALSE	0	TRUE	3	1	5	2
3	FALSE	0	TRUE	3	1	9	2
4	FALSE	12	TRUE	2	2	23	2
3	FALSE	0	TRUE	4	1	7	2
3	FALSE	2	TRUE	4	1	3	2
4	FALSE	0	TRUE	2	2	7	2
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2	TRUE	0	TRUE	4	1		2
3	TRUE	0	TRUE	4	2		2
1	FALSE	0	TRUE	4	1	8	2
4	FALSE	0	TRUE	4	1	2	2
1	FALSE	0	TRUE	2	2	1	1
1	FALSE	0	TRUE	4	2	2	2
4	FALSE	0	TRUE	3	1	14	2
4	FALSE	0	TRUE	5	1	3	2
4	FALSE	0	TRUE	2	2	0	1
1	FALSE	2	TRUE	2	1	7	2
4	FALSE	0	TRUE	2	2	5	2
4	FALSE	0	TRUE	2	2	10	2
4	FALSE	4	TRUE	1	1	3	2
4	TRUE	0	TRUE	4	1		2

3	FALSE	0	TRUE	4	2	5	2
4	FALSE	8	TRUE	2	2	16	2
3	TRUE	0	TRUE	4	1		2
4	FALSE	0	TRUE	2	2	1	1
3	FALSE	0	TRUE	3	1	11	2
4	FALSE	0	TRUE	2	2	20	2
4	TRUE	6	TRUE	1	1		2
4	TRUE	0	TRUE	2	1		2
4	FALSE	0	TRUE	2	1	7	2
4	FALSE	0	TRUE	2	2	16	2
4	FALSE	0	TRUE	3	2	4	2
2	TRUE	13	TRUE	3	2		2
4	FALSE	0	TRUE	2	2	15	2
4	FALSE	2	TRUE	2	2	10	2
3	FALSE	11	TRUE	3	1	4	2
3	FALSE	2	TRUE	2	2	7	2
1	FALSE	4	TRUE	4	1	4	2
1	FALSE	0	TRUE	2	1	4	2
3	TRUE	0	TRUE	2	2		2
4	FALSE	0	TRUE	2	2	8	2
4	FALSE	2	TRUE	1	1	35	2
3	TRUE	6	TRUE	2	1		2
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	TRUE		TRUE	5	2		2
4	TRUE	0	TRUE	3	1		2
1	TRUE	6	TRUE	2	2		2
	FALSE		TRUE	2	2	0	1
3	TRUE	9	TRUE	2	1		2
1	TRUE	0	TRUE	2	2		2
4	FALSE	0	TRUE	4	1	2	2
	TRUE		TRUE	2	2		2
3	FALSE	0	TRUE	2	2	4	2
	TRUE		TRUE	2	1		2

15. ANNEXURE V – IRB FORMS

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD, Ph.D.
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

December 15, 2016

Dr. Geethu Rachel Iype,
PG Registrar,
Department of Surgery- 2,
Christian Medical College,
Vellore - 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma.
Geethu Rachel Iype , Employment Number: 29561, General Surgery, Dr Mark Ranjan Jesudason , Employment Number: 28081, General Surgery- Unit 2, Dr. Anu Eapen, Employment Number: 30125, Radio diagnosis, Dr. Dipti Masih, Employment Number: 32530, Pathology, Dr. Rajat Raghunath, Employment Number: 28850, General Surgery Unit 2, Dr. Gigi Varghese, Employment Number: 51915, General Surgery, Unit 2, Dr. Rajesh Joseph Selvakumar, Employment Number: 32588, General Surgery, Unit 2, Dr.Tunny Sebastian, Employment Number: 32291, Biostatistics,.

Ref: IRB Min No: 10362 [OBSERVE] dated 03.11.2016

Dear Dr. Geethu Rachel Iype,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

Cc: Dr Mark Ranjan Jesudason, Dept. of Surgery- 2, CMC, Vellore

1 of 4

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

December 15, 2016

Dr. Geethu Rachel Iype,
PG Registrar,
Department of Surgery- 2,
Christian Medical College,
Vellore - 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma.
Geethu Rachel Iype , Employment Number: 29561, General Surgery, Dr Mark Ranjan Jesudason , Employment Number: 28081, General Surgery- Unit 2, Dr. Anu Eapen, Employment Number: 30125, Radio diagnosis, Dr. Dipti Masih, Employment Number: 32530, Pathology, Dr. Rajat Raghunath, Employment Number: 28850, General Surgery Unit 2, Dr. Gigi Varghese, Employment Number: 51915, General Surgery, Unit 2, Dr. Rajesh Joseph Selvakumar, Employment Number: 32588, General Surgery, Unit 2, Dr.Tunny Sebastian, Employment Number: 32291, Biostatistics,.

Ref: IRB Min No: 10362 [OBSERVE] dated 03.11.2016

Dear Dr. Geethu Rachel Iype,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma" on November 03rd 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Proforma
3. Information Sheet and Informed Consent Form (English, Tamil, Hindi, Malayalam, Bengali)
4. Cvs of Drs. Geethu Rachel Iype, Mark Ranjan Jesudason, Anu Eapen, Dipti Masih, Rajat Raghunath, Gigi Varghese, Rajesh Joseph Selvakumar, Tunny Sebastian.
5. No. of documents 1 - 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

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The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 03rd 2016 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Rekha Pai	BSc. MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal,Basic Medical Scientist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician

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Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Sneha Varkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Assessment of factors that predict a positive Circumferential Resection Margin (CRM) in rectal adenocarcinoma" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation

A sum of 5,000/- INR (Rupees Five thousand Only) will be granted for 2 years.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

IRB Min No: 10362 [OBSERVE] dated 03.11.2016

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